# EXHIBIT 17

OIPE JC139 APR 1 1 2005 PATENT & TRADEMARK OFFICE

## Affidavit by Edith Mathiowitz, Ph.D.

I, Edith Mathiowitz, declare and state as follows:

**J. Relevant Expertise**

1. That I currently hold joint appointments at Brown University as Professor of Medical Science and Engineering, Department of Molecular Pharmacology & Biotechnology and as Professor of Engineering, and that I also am the Director of Graduate Program, Artificial Organs, Biomaterials and Cellular Technology.

2. That separate from my University appointments, I am currently a Consultant to and a Board Member of and previously held the positions of Chairwoman and President of Spherics, a start up company involved in drug design and drug formulation which I founded.

3. That I am well qualified to give an opinion concerning the subject matter that is claimed in the above-identified patent application which relates to controlled-release preparations of diltiazem that are designed for once-daily evening dosing (chronotherapeutic compositions).

4. That my relevant expertise is substantiated by my Curriculum Vitae which is attached as Exhibit 1 to this Affidavit. Relevant areas of my expertise which are substantiated by information contained in the Curriculum Vitae are enumerated below.

5. That for example I have substantial expertise and experience in the development of encapsulated drugs which provide for sustained, controlled release upon in vivo oral administration.



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6. That I further have substantial experience in polymer chemistry and particularly the design and/or selection of biocompatible polymers appropriate for drug encapsulation which provide for desired release characteristics upon in vivo administration.

7. That I frequently am invited to speak on the subject of drug delivery systems, am the lead author on many papers on this subject, and further teach courses relating to drug delivery systems and polymers for use therein at Brown University. I am also currently one of the organizers of the Controlled Release Society.

8. That I further am an inventor on numerous patents relating to drug delivery formulations, drug containing microspheres, and polymers for use therein.

9. That based on my expertise in the art, Biovail Incorporated ("Biovail") asked that I provide my opinion concerning the subject matter claimed in patent applications 09/565,451 ("'451 Application") and 09/465,338 ("'338 Application") or "Biovail applications".

**K. Summary of Documents Reviewed**

10. That as part of this review I was provided and reviewed copies of the above-identified Biovail patent applications; a listing of the current claims in both of these patent applications; copies of two patent documents which were cited as prior art against these applications, *i.e.*, EP0856313, which is assigned to Elan Corporation PLC and which names Edward James Geoghegan

et al the lead as inventor ("the '313 application or EP '313) (Exhibit 2) and WO93/00093 which is assigned to Biovail and names Arthur Deboeck et al. as the lead inventor ("the '093 Application" "WO '093") (Exhibit 3); copies of Office Actions issued by the United States Patent and Trademark Office in connection with these applications including the most recent final Office Actions wherein prior art rejections were maintained against the Biovail application claims based on the '313 Application and the '093 Application; and Biovail's responses to such Office Actions.

11. That I was further provided and reviewed technical materials identifying the exact composition of Biovail's commercial embodiments of the subject invention which comprise chronotherapeutic controlled-release preparations of diltiazem currently marketed by Biovail under the Tradename Diltiazem LA® (Exhibit 4).

12. That I further was provided and reviewed a set of proposed amended claims (Exhibit 5) which I understand are to be filed together with this Afffidavit and which will replace all of the current claims contained in the subject Biovail applications. These amended claims consolidate the subject matter claimed in the Biovail '451 and '338 applications.

13. That I further was provided and reviewed a description of in vivo studies involving the administration of a diltiazem formulation corresponding to the claims being pursued in the subject Biovail patent applications (Diltiazem LA®); as well as sustained release diltiazem formulations corresponding to the patent applications cited against the subject

Biovail claims, *i.e.,* the '093 and the '313 patent applications, wherein each of these diltiazem formulations was administered under similar conditions in the evening. (Exhibit 6 and Exhibit 7) The fact that the comparative formulations (respectively Cardiazem CD® and Tiazac®) correspond to the diltiazem formulations disclosed in the cited patent publications is evidenced by the Food and Drug Administration Orange Book listings for Cardiazem CD® and Tiazac® (Exhibit 8 and Exhibit 9) which identify United States patents 5,002,776 and 5,529,791 (which are US counterparts respectively of EP '313 and WO '093) as being US patents which cover these commercially available Diltiazem drug formulations (*See* Exhibit 8 and Exhibit 9). Additionally, I reviewed an exhibit containing a side-by-side comparison of the exact constituents of diltiazem formulations according to the invention (Diltiazem LA®) and diltiazem compositions according to the cited references (EP '313 and WO '093, Cardiazem CD® and Tiazac®, respectively. (Exhibit 10). Further, I reviewed another exhibit containing a side-by-side comparison of the results of in vivo studies comparing the pharmacokinetic properties of these same diltiazem formulations. (Exhibit 11) The exhibits containing these side-by-side comparisons (Exhibit 10 and Exhibit 11) were prepared at the request of Examiner Kishore at a recent interview attended by me.

14. That I further was provided and reviewed a published clinical study evaluating the clinical efficacy of a chronotherapeutic controlled release diltiazem formulation corresponding to the chronotherapeutic diltiazem formulations and methods of use being claimed by Biovail in the patent

applications at issue. This clinical study is contained in a peer-reviewed publication entitled "Efficacy and Safety of a Once Daily Graded-Release Diltiazem Formulation in Essential Hypertension", *Amer. J. Hypertension, Ltd.*, 16:51-58 (2003) (Exhibit 12).

### L. Summary of Subject Matter Being Claimed in Subject Biovail Patent Applications

15. That based on the documents I reviewed, I understand that the subject matter disclosed and claimed in both of the Biovail patent applications at issue relates to orally administrable chronotherapeutic controlled-release preparations containing a pharmaceutically acceptable chronotherapeutic form of diltiazem designed for once daily administration in the evening. (*See* Exhibit 4).

16. That I understand that upon entry of the proposed amendment (Exhibit 5) which consolidates the subject matter being claimed in the Biovail '451 and '338 patent applications (which is to be submitted together with this Affidavit), all of the pending claims will require the following:

> a controlled-release orally administrable preparation comprising at least one pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours, the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the said at least one coating covering the core comprising a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating being

comprised of (i) constituents selected from at least one lubricant and/or at least one hydrophilic polymer and (ii) further comprising as an essential constituent at least one water insoluble swellable neutral copolymer; and wherein the amount of said water swellable and diffusible coating and the specific rations of said constituents (i) and (ii), which comprise said water swellable and diffusible coating covering said diltiazem containing core contained in said at least one bead, are formulated such that the orally administrable composition:

A) in vitro exhibits the following in vitro release characteristics;

(i) releases the diltiazem or a pharmaceutically acceptable salt thereof into a aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours;

(e) in excess of about 75% after 24 hours;

and/or (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

(a) between about 1% and about 25% after 2 hours;

(b) between about 7% and about 45% after 4 hours;

(c) between about 30% and about 68% after 8 hours;

(e) in excess of about 75% after 24 hours;

and wherein said in vitro release characteristics further result in an orally administrable composition that:

B) when given to humans exhibits the following properties:

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria:

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria: and

(iiii) providing a Cmax of diltiazem in the blood at between about 10 and 15 hours after oral administration.

17. Therefore, upon entry of this amendment (Exhibit 5) all of the Biovail claims will be directed to orally administrable chronotherapeutic once-daily controlled-release diltiazem formulations and methods of use wherein said diltiazem is comprised in a core which is encapsulated in a bead coated with an amount of a water swellable and diffusible coating that is comprised of specific constituents, including in particular at least one water insoluble swellable neutral copolymer. Additionally, all the Biovail claims will further require that the amount of this water swellable diffusible coating and the specific constituents contained therein and ratios thereof are formulated such that the resultant diltiazem formulation possesses a specific combination of in vivo properties, *i.e.,* (i) Cmax occurs about between 10 and 15 hours after evening administration, (ii) higher bioavailability when given at night and (iii) bioequivalence when given in the morning with or without food. Still further, all of the Biovail claims will require that such compositions possess defined in vitro dissolution properties over the time of administration (24 hours) in two different medium aqueous and buffered medium having pH ranging from 5.5 to 6.5). It has been unexpectedly discovered by Biovail that the incorporation of an appropriate amount of a water swellable, diffusible coating, comprised of the

constituents recited in the claims, in particular including a water insoluble swellable neutral copolymer results in diltiazem formulations possessing vitro dissolution properties and further <u>that these in vitro dissolution properties reproducibly correlate to diltiazem formulations possessing the recited in vivo properties, which render the Biovail diltiazem formulations exquisitely suited for chronotherapeutic use</u>. In my opinion, the prior art does not suggest diltiazem compositions having the advantageous properties of the Biovial compositions which are evidenced by in vivo comparative studies of record and discussed herein.

18. That, with respect to such in vivo studies, in my opinion, Biovail's commercial embodiment (Cardiazem LA®) (*See* Exhibit 4), which was compared to the prior art Diltiazem formulations is representative of <u>all</u> the claims currently being pursued by Biovail in the '451 and '338 patent applications, as well as the subject matter that is to be claimed upon entry of the proposed amendments. (*See* Exhibit 5). Cardiazem LA® is representative of the claimed invention as it contains all constituents required by the Biovail claims (See Exhibit 4) and possesses the specific in vitro dissolution and in vivo pharmacokinetic properties required by the Biovail claims.

**M. <u>Comparison of Prior Art Controlled Release Diltiazem Formulations to Biovail Controlled Release Diltiazem Formulations</u>**

19. That for the reasons set forth *infra*, it is my expert opinion that neither the '313 Application nor the '093 Application teaches a chronotherapeutic controlled release diltiazem formulation containing a water

swellable and diffusible coating surrounding a diltiazem containing core comprised of specific constituents, in particular including a water insoluble swellable neutral copolymer, wherein the ratios of such constituents, and the amount of said water swellable and diffusible coating surrounding the diltiazem containing core are selected such that the resultant orally administrable composition possesses the specific combination of in vitro and in vivo properties of the chronotherapeutic controlled release diltiazem formulations and methods of use being claimed by Biovail in the subject patent applications.

20. That it is further my expert opinion that the '313 and '093 patent applications, considered alone or in combination, fail to provide any explicit or implicit teaching which would motivate or enable a skilled artisan to modify the controlled release diltiazem compositions disclosed in the '313 or '093 patent applications, in particularly to modify the coating layer described therein, *e.g.*, by variation of the polymeric constituents, ratios thereof, and/or amount of the coating layer in order to produce a controlled-release formulation of diltiazem possessing the novel combination of in vitro and in vivo properties of the orally administrable chronotherapeutic controlled-release diltiazem formulations claimed by Biovail. Particularly, I have carefully reviewed both the EP '313 and WO '093 patent disclosures and based on this review, I am of the opinion that these references alone or in combination provide no explicit or implicit incentive to produce a diltiazem formulation having the novel combination of in vitro and in vivo properties being claimed by Biovail in the patent applications at issue.

21. That more specifically, it is my expert opinion that the in vivo pharmacokinetic studies of record in the Biovail patent application which compared evening administration of a diltiazem controlled release formulation according to the Biovail invention (Diltiazem LA®) to the prior art (Cardiazem CD® (Exhibit 6), which is a commercially available controlled-release diltiazem formulation which corresponds to EP '313) and Tiazac® (Exhibit 7) (which is a commercially available chronotherapeutic controlled-release diltiazem according to WO '093) provides convincing and irrefutable evidence that the controlled-release diltiazem compositions being claimed by Biovail possess very different and clearly superior in vivo and in vitro characteristics vis-à-vis the prior art diltiazem formulations. The results of these pharmacokinetic studies are contained in Exhibit 6 and Exhibit 7 to this Affidavit and were previously submitted during prosecution of the subject Biovail applications at issue herein. Additionally, at the request of Examiner Kishorc, these pharmacokinetic comparisons are further consolidated in a single exhibit, newly submitted herewith, which is attached to this Affidavit as Exhibit 11.

22. Particularly, I note that the in vivo studies (contained in Exhibit 6 and Exhibit 11), which compared evening administration of the EP' 313 formulation (Cardiazem CD®) to a formulation according to the Biovail claims (Cardiazem LA®), revealed the following significant pharmacokinetic differences between these controlled release diltiazem formulations:

(i) That the Cmax for the Biovail composition, when dosed in the evening, according to prescribed guidelines, occurred

much later (around 11 hours after evening administration) than for Cardiazem CD®, at a time when the risk of cardiac events and stroke are at their most elevated. By contrast, when dosed in the evening, Cardiazem CD® resulted in Cmax occurring 6 hours after administration.

(ii) That when the pharmacokinetic data was converted to Night/Day ratios that the pharmacokinetics of the Biovail Cardiazem LA® formulation is much better than that of Cardiazem CD® (EP '313 formulation);

(iii) That further, the Biovail Cardiazem LA® formulation provided for much higher bioavailability when dosed in the evening (*See* Table 1 and 2, AUC Night/Day rate >1) (Exhibit 6). By contrast, the Cardiazem CD® formulation exhibited lower bioavailability when dosed in the evening (*See* Table 1 and 2, AUC Night/Day rate is <1 in Exhibit 6, and Exhibit 11);

(iv) That still further the Biovail Cardiazem LA® formulation provided for much lower plasma fluctuation than the Cardiazem CD® (EP '313 formulation); and

(v) That the Biovail Cardiazem LA® composition resulted in a higher Cmax when dosed in the evening than Cardiazem CD® (*See* Tables 1 and 2, Exhibit 6 and Exhibit 11).

23. That in my opinion these enumerated significant pharmacokinetic differences provide convincing evidence as to the substantial

and non-obvious differences between the subject Biovail controlled release diltiazem formulations as compared to diltiazem formulations according to EP '313 (Cardiazem CD®). I base my opinion most especially upon the fact that both of these compositions were administered in the evening under appropriate side-by-side comparison conditions. In my opinion, it is truly unexpected that the subject chronotherapeutic diltiazem composition possesses such very different pharmacokinetic properties when administered in the evening in comparison to the EP '313 formulation.

24. I further note that the in vivo studies ( the results of which are contained in Exhibit 7 and Exhibit 11), which compared administration of Tiazac®, the commercial embodiment of the controlled-release diltiazem formulation disclosed in WO '093) to the Biovail chronotherapeutic diltiazem composition (Cardiezem LA®) corresponding to the claims at issue herein, again when both diltiazem formulations were administered under similar conditions in the evening, revealed the following significant pharmacokinetic differences between the subject Biovail Cardiazem LA® composition as compared to a controlled release diltiazem formulation according to WO' 093 (Tiazac®, another Biovail diltiazem formulation which is not a chronotherapeutic formulation):

(i) That when dosed in the evening the subject Biovail composition (Cardiazem LA®) resulted in Cmax diltiazem levels peaking about 11 hours after administration, *i.e.*, diltiazem levels in the blood are the highest in the early morning hours when the risk of sudden cardiac events and stroke are similarly at their highest. By contrast, the

Tiazac® formulation (WO'093) when administered in the evening resulted in Cmax diltiazem levels occurring only about 6 hours after administration, *i.e.*, diltiazem levels in the blood peak much earlier, at a time when the risk of sudden cardiac events and strokes are not at their highest;

(ii) That a lower Cmax is achieved for Tiazac® than Cardiazem LA® when both are dosed in the evening (*See* data contained in Figure 3 and Table 3 and 4 contained in Exhibit 7 and Exhibit 11) and that the Cmax Night/Day Ratio for Tiazac® is <1 whereas for Cardiazem CD® it is >1;

(iii) That Tiazac® exhibits a higher plasma fluctuation and therefore potentially could elicit more adverse affects in patients compared to Cardiazem LA® (*See* data in Table 4 contained in Exhibit 7 and Exhibit 11); and

(iv) That Tiazac® results in a lower bioavailability when dosed in the evening compared to Cardiazem LA® (*See* Tables 3 and 4, Exhibit 7 and Exhibit 11 which show that the AUC Night/Day ratio for Tiazac® is <1 whereas for the subject chronotherapeutic formulation (Cardiazem LA® ) it is >1).

25. That in my expert opinion the above-enumerated pharmacokinetic differences between the subject Biovail chronotherapeutic controlled-release diltiazem formulation and a diltiazem formulation according

to WO' 093 provide convincing evidence as to the substantial and non-obvious differences between the subject chronotherapeutic diltiazem controlled release composition and diltiazem formulations according to WO '093. I again base my conclusions upon the fact that when both of these compositions were administered in the evening under appropriate side-by-side comparison conditions that they exhibited dramatically different pharmacokinetic properties. I believe it to be truly unexpected that the subject chronotherapeutic compositions possess such very different pharmacokinetic properties when administered under similar evening conditions. In my opinion, compositions possessing such advantageous properties are not suggested by the prior art.

26. With respect to my opinion, I further acknowledge the fact that the enhanced properties of the Biovail chronotherapeutic formulations at issue herein are apparently achieved by the nature and amount of the water swellable and diffusible coating surrounding the diltiazem drug core, which includes as an essential element at least one water insoluble, swellable neutral co-polymer, and that this water swellable, diffusible coating apparently provides for sustained pH-independent release of diltiazem from the drug containing core after administration when it is in contact with gastrointestinal fluids. I further understand based on my review of the provided relevant excerpts of the Biovail prosecution histories that the Examiner has concluded that it allegedly would have been obvious based on the cited prior art to have modified the formulations disclosed therein, in particular to modify the nature of the coating layer surrounding the diltiazem coating core, in order to obtain a water swellable,

diffusible coating containing at least one water insoluble, swellable polymer and thereby obtain a controlled-release diltiazem formulation possessing the enhanced pharmacokinetic properties of the claimed invention. I respectfully but vigorously disagree.

27. That I vigorously disagree because in my opinion neither EP '313 nor WO '093 provides any teaching or suggestion regarding the problem addressed and solved by Biovail, namely the production of a truly chronotherapeutic diltiazem formulation, *i.e.,* one which when administered in the evening every 24 hours results in enhanced pharmacokinetic properties, most especially Cmax diltiazem levels being attained in the early morning hours when the risk of sudden cardiac events and stroke are at their most elevated. Both of the cited publications are completely silent with respect to a chronotherapeutic composition possessing such properties or the need and intrinsic advantages of a diltiazem formulation possessing such properties.

28. That even assuming that the cited publications were not silent with respect to the problems solved by the present invention, contrary to the position taken by the Patent Office, it is my opinion, based on my substantial relevant experience in drug formulation and expertise in polymer chemistry and the use thereof in drug coatings, it could not have been reasonably anticipated that the incorporation of a sufficient amount of a coating layer comprising at least one water insoluble swellable neutral co-polymer (*e.g.*, a water-, acid, base-insoluble polymer of a neutral acrylic polymer; a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate; or a neutral copolymer without any

functional groups that form water insoluble films) would have resulted in a chronotherapeutic diltiazem formulation possessing the novel and superior pharmacokinetic properties of the subject chronotherapeutic diltiazem formulations.

29. That my opinion is supported by my substantial experience in drug formulation and drug encapsulation techniques, as well as the design and selection of polymers for use in sustained release drug formulations having desired in vivo pharmacokinetic properties and in vitro release properties. That my experience has instead shown that the formulation of orally administrable sustained release drug formulations possessing a requisite combination of in vitro dissolution properties and in vivo pharmacokinetic properties is highly complex and unpredictable. For example, whereas one drug encapsulation system may achieve desired pharmacokinetic properties for a particular drug, it may be totally unsuitable for another drug, or may need to be substantially modified. Also, I can well attest to the fact that in vitro dissolution properties for a particular drug formulation do not necessarily or predictably correlate to desired in vivo pharmacokinetic properties. By contrast, the design of a drug delivery system which achieves a desired combination of in vitro dissolution characteristics which correlate to desired in vivo pharmacokinetic properties typically requires much trial and error experimentation, *e.g.*, variation of polymeric and/or other constituents that constitute the coating layer or layers, variation of the amounts thereof, variation of the active particle size, variation of the amount of encapsulated active, variation of formulation methods, and the

like, and systematically evaluating whether any of such variations result in an orally administrable drug formulation possessing desired in vitro dissolution properties and in vivo properties.

30. That based on the unpredictability and complexity generally associated with the design of sustained drug delivery formulations having a desired set of in vitro and in vivo properties, it is my opinion that while it might have been "obvious to try" to vary the polymers and other constituents in the coating material, the ratios thereof, and/or the amount of the coating layer, that the effects of such modifications on in vitro release characteristics and in vivo pharmacokinetic properties of the resultant diltiazem formulation were far from obvious.

31. That it further is my expert opinion that EP '313 provides no motivation to substitute a neutral copolymer for any of the charged copolymers contained in the EP '313 diltiazem formulation. With respect thereto, the Table (Exhibit 13), submitted during prosecution of the Biovail applications at issue reveals that every Eudragit co-polymer mentioned in EP '313 is a charged co-polymer. Moreover, as shown in the attached pages from the Handbook of Pharmaceutical Excipients, Fourth Edition, Edited by Raymond C. Rowe et al., 2003 (Exhibit 14), it can be seen that <u>all</u> of the specific Eugragit copolymers exemplified in EP '313 are charged in the pH range inherent to the gastrointestinal tract. (*See especially* pages 463-465 of Exhibit 14). Moreover, based on my review of the reference, EP '313 provides no suggestion to substitute the exemplified charged Eudragit copolymer with an uncharged copolymer which

provides for pH-independent drug release as contained in the Biovail diltiazem formulations. Moreover, I disagree with the Patent Officials' position that EP'313 would generically suggest all types of Eudragit copolymers, including neutral co-polymers. To the contrary, one skilled in the relevant art such as myself, reading the EP'313 disclosure, would instead conclude that their invention requires the use of a charged Eudragit copolymer. My conclusion is supported by the fact that neutral and charged copolymers are not equivalent and do not provide equivalent results. By contrast, the water insoluble, swellable neutral co-polymer which is contained in the coating layer that surrounds the drug containing core in the subject diltiazem formulations, because of its neutral uncharged nature, results in a diffusible coating layer that facilitates prolonged pH–independent release of the drug from the drug containing core when it is in contact with gastrointestinal fluids. This pH–independent drug release in turn facilitates the desired result, *i.e.*, Cmax levels of diltiazem being attained after evening administration in the morning hours when cardiac events are most likely to occur. However, while this outcome was hoped for, it was hardly reasonably anticipated given the highly complex and numerous unpredictable factors that are associated with the design of sustained release drug delivery compositions possessing a desired set of in vitro and in vivo properties. In my opinion, it is not suggested by EP '313, nor could it have been reasonably anticipated that the incorporation of a neutral co-polymer in the coating layers in lieu of a charged co-polymer would have resulted in chronotherapeutic diltiazem formulations possessing the novel combination of in

vitro and in vivo characteristics possessed by the Biovail claimed invention, which differ dramatically from diltiazem formulations according to EP'313.

32. I also understand that the Examiner at the recent interview criticized the fact that only one water insoluble, swellable neutral co-polymer was exemplified in the subject application. The Examiner seemed to question whether a skilled artisan would be able to select other appropriate water insoluble, swellable neutral co-polymers suitable for use in the Biovail invention. With respect thereto, it is my expert opinion that a skilled artisan, based on the teachings of the subject application, would be able to select other suitable water swellable neutral co-polymers and obtain diltiazem formulations having the desired combinations of in vitro and in vivo pharmacokinetic properties. For example, I am aware of Kollicoat® SR 30D, another water insoluble swellable neutral co-polymer, commercially available from BASF, that it biocompatible and which is suitable for use in coatings and sustained-release coated drug formulations. (*See* Exhibits 15 and 16).

33. I also understand with respect to the showing of unexpected results contained in Exhibit 6 and Exhibit 11 that the Examiner has suggested that the comparative results are not commensurate in scope with the claims and further do not constitute an appropriate comparison because the dosage of diltiazem in the Biovail Cardiazem LA® composition is not the same as the comparison composition (Cardiazem CD®). I respectfully disagree.

34. I have reviewed all of the Biovail claims and compared these claims to the description of the commercial Biovail formulation used in the

comparison (Cardiazem LA®). (*See* Exhibit 4 and Exhibit 5). In my opinion, the exemplified Cardiazem LA® formulation corresponds to and is representative of all of the claims being pursued by Biovail.

35. That I further understand from my review of the prosecution history that the Examiner has concluded that the in vitro release characteristics of the claimed chronotherapeutic compositions (as recited in the Proposed Amended Claims) corresponds to that possessed by the prior art. I vigorously disagree. In my opinion, the dissolution ranges recited in the claims at issue herein clearly show that the claimed chronotherapeutic compositions possess very different dissolution properties in two different media, i.e., an aqueous medium and a buffered medium having a pH which ranges from pH 5.5 to 6.5. These differences are illustrated by the dissolution data of record comparing the dissolution profile of a Diltiazem formulation according to the claims (Cardiazem LA) to a Diltiazem formulation according to the prior art (Cardiazem CD and Tiazac). This data was obtained in two different media using the same in vitro dissolution testing procedures specified in the claims at issue. In my opinion this data establishes unequivocably that there exists clear and significant differences between the in vitro dissolution profiles of the subject chronotherapeutic diltiazem formulations versus the prior art diltiazem formulations. Furthermore this data supports Applicants' arguments made during prosecution that it is improper to compare dissolution profiles conducted in different dissolution media having different pH ranges as they often differ dramatically. Indeed this is why when orally administrable sustained release formulations are produced that

their dissolution properties must be tested in different dissolution media so as to take into account the disparate pH conditions inherent to the GI tract.

36. That I further believe that the provided comparison establishes that the advantages achieved by the Biovail composition are not a function of increased dosage or potency. In fact, in the provided comparison (Exhibit 6) Biovail clearly states that in order to "normalize for the difference in dosage strength of the two diltiazem formulations" the data was presented "as Night/Day ratios" This is similarly clear from Exhibit 11. Therefore, it is apparent based on the in vivo pharmacokinetic comparative studies already of record and newly submitted in Exhibit 11 that the enhanced pharmacokinetic properties of the Biovail formulation (as exemplified by Cardiazem LA®) relative to the EP '313 composition (Cardiazem CD®) are not attributable to the administration of a higher diltiazem dose as suggested by Patent Examiner. Rather, as discussed above, the enhanced results are believed to be attributable to the combination of constituents contained in the coating layer comprised in the claimed sustained release diltiazem formulations, in particular the swellable neutral copolymer, as well as the formulation and amount of such coating layer relative to other constituents in the subject diltiazem formulations.

N. **The Prior Art Rejections Should Be Withdrawn Because the Subject Invention Achieves Results Which Correlate to Enhanced Clinical Efficacy**

37. For the reasons enumerated above, it is my expert opinion that neither EP '313 nor WO '093 teaches or provides the requisite motivation to produce a truly chronotherapeutic diltiazem controlled release composition,

which when administered in the evening, every 24 hours, exhibits the combination of in vitro and in vivo properties recited in the Biovail claims. In my opinion, the enhanced properties of the Biovail compositions vis-à-vis the prior art are highly significant since these differences result in a diltiazem medicament which exhibits greater clinical efficacy, *i.e.*, a medicament which should elicit reduced side effects (because of lower blood plasma fluctuation) and which medicament should better prevent sudden heart events and stroke in patients when the risks are at their most elevated. As noted previously, in my opinion, it has been abundantly demonstrated that the administration of a Biovail diltiazem formulation as claimed herein results in Cmax diltiazem levels peaking in the early morning (when administered in the evening, as directed), *i.e.*, about 10-15 hours after administration. The enhanced clinical efficacy of the subject Biovail diltiazem formulations (which I believe to be attributable to the nature and amount of the coating layer) is further apparent from the clinical study contained in Exhibit 12 which compared the efficacy and safety of a chronotherapeutic diltiazem formulation according to the Biovail claims (Diltiazem LA®) at different dosages (120, 240, 360 and 540 mg amounts) administered at bedtime in a 7-week randomized, double-bind comparison to a placebo, and the same formulations administered once-daily in the morning (8 AM).

38. The results of this clinical study revealed that subjects administered the inventive chronotherapeutic diltiazem according to the invention in the evening exhibited dose-related mean reductions in mean

diastolic blood pressure between 6 AM and 12 noon compared to morning administration, as well as exhibiting similar reductions in systolic blood pressure. Based on these results, the authors of this study concluded that administration of Biovail's chronotherapeutic compositions as directed in the evening obtained greater reduction of blood pressure in the early morning hours (between 6 AM and 12 noon) when circadin blood pressure is at its highest, and furthermore provides a safe, well tolerated therapeutic option for patients with severe hypertension. Given the well known correlation of hypertension to the onset of sudden cardiac events and stroke, this study provides compelling evidence that the present invention provides controlled release diltiazem formulations having enhanced clinical efficacy, which should correlate to a reduction of heart attacks and stroke in patients using the Biovail claimed compositions according to the prescribed guidelines (evening administration). This is a very significant result which can not be down played because such adverse events can often be fatal or life threatening. Therefore, for the reasons set forth herein, it is my opinion that the chronotherapeutic controlled release diltiazem formulations which are claimed in the subject Biovail patent applications provide a significant advance in the art which has resulted in improved therapies for the prevention of heart attack and other adverse cardiac events.

**O. <u>The Prior Art Rejections Should Further Be Withdrawn Based on Additional Secondary Considerations (Commercial Success)</u>**

39. I further note that the unexpected results and advantages of the subject Biovail orally administrable chronotherapeutic diltiazem

formulations are evidenced by commercial success. In particular I understand that the annual sales for Cardiazem LA® in 2003 were $47.7 million whereas in 2004 they went up to $54.3 million dollars, *i.e.*, a 14% increase in sales from the prior year (which correlates to about 1,350,000 prescriptions annually). In my opinion the high sales and increasing number of prescriptions of Diltiazem LA® can be attributed to the enhanced pharmacokinetic and clinical properties of this diltiazem formulation vis-à-vis other commercially available diltiazem formulations for the reasons discussed supra.

40. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Date: 4/10/05

By: Edith Mathiowitz

Edith Mathiowitz, Ph.D.

360619

**EXHIBIT LIST**

1. Curriculum Vitae Edith Mathiowitz Ph.D.
2. EP0856313, assigned to Elan Corporation and naming Edward James Geoghegan as lead inventor.
3. WO93/00093, assigned to Biovail Incorporated and naming Arthur Deboeck as lead inventor.
4. Description of Diltiazem LA®
5. Listing of Amended Claims
6. Comparison of Pharmacokinetic Properties of Diltiazem Formulation According to EP'313 (Cardiazem CD®) and Subject Invention (Diltiazem LA®)
7. Comparison of Pharmacokinetic Properties of Diltiazem Formulation According to the Invention (Diltiazem LA®) and Diltiazem Formulation According to WO'093 (Tiazac®)
8. FDA Orange Book Listing for Cardiazem LA®
9. FDA Orange Book Listing for Tiazac®
10. Comparison of the Constituents Comprising Diltiazem Formulation According to the Invention and Prior Art Diltiazem Formulations.
11. Comparison of the Pharmacokinetic Properties of Diltiazem Formulation According to the Invention and Prior Art Diltiazem Formulations Administered Under Appropriate Side-by-Side Conditions
12. "Efficacy and Safety of a Once Daily Graded-Release Diltiazem Formulation in Essential Hypertension" Amer. J. Hypertension, Ltd., 16:51-58
13. Table Showing the Charged Nature of All Eudragit Co-Polymers Disclosed in EP'313
14. Handbook of Pharmaceutical Excipients, Fourth Edition, Edited by Raymond C. Rowe et al. (2003)
15. "Kollicoat® SR 30D," Exact Excipients & Actives for Pharma, 11; Oct 2003, p. 2
16. "Kollicoat® 3R 30D", Technical Information, January 2004, BASF Fine Chemicals, ¶ 1-3

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# Edith Mathiowitz

## Curriculum Vitae

### Education

| | |
|---|---|
| 1985 | **Weizmann Institute of Science, Israel.** Ph.D. in Physical Chemistry. Thesis Advisor: Prof. M.D. Cohen, Head of the Structural Chemistry Department. |
| 1979 | **Weizmann Institute of Science, Israel.** M.Sc. in Physical Chemistry. |
| 1973 | **Tel Aviv University, Tel Aviv, Israel.** B.Sc. in Chemistry. |

### Awards

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|---|---|
| 2000 | The Eurand Award for **Excellence in Research in the Area of Oral Drug Delivery Systems.** |
| 1994 | **Recognition Award for Excellence in Guiding Graduate Student Research.** Controlled Release Society - Procter & Gamble. Awarded in Nice, France. |
| 1991-1993 | **Whitaker Foundation Award.** |
| 1985-1987 | **Bantrell Postdoctoral Fellowship** (MIT). A competitive award at MIT in the field of surface science. |
| 1979-1984 | **Feinberg Fellowship, Weizmann Institute of Science, Israel.** A competitive award conferred for graduate research students. |
| 1982 | **Delek Prize** for distinctive research work (Weizmann Institute of Science, Israel). |
| 1973 | **Distinction Prize for B.Sc. students** (Tel Aviv University, Israel). |

**Previous Positions and Professional Experience**

| | |
|---|---|
| 1999- present | Professor of Medical Science and Engineering, Department of Molecular Pharmacology & Biotechnology, Director of Graduate Program, Artificial Organs, Biomaterials and Cellular Technology. Box B-G393, Providence, RI 02912. Tel (401) 863-1358. Fax (401) 863-1753. |
| 1999-present | Chair woman and consultant, Spherics. |
| 1997-1999 | President of a start up company, Spherics. |
| 1994-1999 | Associate Professor of Medical Science and Engineering, Department of Molecular Pharmacology & Biotechnology, Director of Graduate Program, Artificial Organs, Biomaterials and Cellular Technology. Box B-G393, Providence, RI 02912. Tel (401) 863-1358. Fax (401) 863-1753. |
| 1994-Present | Joint appointment: Associate Professor of Engineering. |
| 1991-1994 | Assistant Professor of Medical Science, Director of Graduate Students, Division of Biology and Medicine, Section of Artificial Organs, Biomaterials and Cellular Technology. |
| 1989-1991 | Senior Research Scientist in Drug Delivery. In charge of microencapsulation and new polymer development. Enzytech, Inc. 763 D Concord Avenue, Cambridge, MA 02138. Tel. (617) 252-0001/210. Fax: (617) 252-0915. |
| 1987-1991 | Visiting Scientist at the Department of Chemical Engineering, MIT. Department of Chemical Engineering, Massachusetts Institute of Technology Cambridge, MA 02139, Tel. (617) 253-3443 |
| 1987-1989 | Research Associate at the Department of Surgery, Children's Hospital, Harvard Medical School. |
| 1984-1986 | Postdoctoral Fellow at the Department of Applied Biological Sciences, with Prof. R. Langer. Subject of research: "Development of erodible systems for drug delivery". |
| 1985-1986 | Lecturer, Pharmacological Engineering, course 20.S35, MIT |
| 1979-1984 | Research student at the Department of Structural Chemistry, Weizmann Institute of Science, with Prof. M.D. Cohen and the late |

Dr. A. Raziel. Subject: "Controlled photochemical rupture of microcapsules".

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|---|---|
| 1975-1979 | Research chemist at the Israel Institute of Biological Research, Nes Ziona, Israel, Polymer Department, in collaboration with the late Dr. A. Raziel, on applied polymer research. |
| 1976-1979 | M.Sc. degree as an external student at the Weizmann Institute of Science with Prof. M.D. Cohen and the late Dr. A. Raziel on "Release of the contents of microcapsules through controlled rupture by a photochemical method". |
| 1973-1975 | Army service in the Medical Corps (chemistry), as a lieutenant. |
| 1973 | Summer student at Prof. G. Navon's Laboratory, Tel Aviv University: " Energy transfer between rare earth metals and phenyl-alanine, in children with phenyl-ketonuria". |

**Teaching Experience**

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|---|---|
| 1992-present | Annual speaker in a short course entitled "Formulation Development of Therapeutic Proteins and Drug Delivery Systems For Peptides and Protein Drugs. Controlled Release Systems for Proteins." organized by the American Chemical Society. Chicago, Illinois. |
| 1992-present | Teaching Bio 211, "Biomaterials," graduate level course. Biomaterials course is an overview of materials considered biocompatible. |
| 1991-present | Teaching Bio 109, "Polymers for Artificial Organs" an undergraduate/graduate level course serving as an introduction to polymer science. |
| 1990 | Lecturer in course on microencapsulation. "Microencapsulation and Nanoencapsulation - Process and Pharmaceutical Applications", Sponsored by the Controlled Release Society, Boston, May 14-15, 1990. |
| 1979-1981 | Lecturer of chemistry at the "Reali" Gymnasium, Rishon Le Zion, Israel. |
| 1974-1975 | Physics and chemistry lecturer in an adult education program at Israel Institute of Biological Research, Nes Ziona, Israel. |

**Professional Organizations**

Controlled Release Society
American Chemical Society (Polymer Division)
American Association for the Advancement of Science
Material Research Society
Biomaterials Society
American Society for Artificial Internal Organs (ASAIO)

**Chair Positions**

1. Session Chair, Annual Meeting of the Society for Biomaterials, May, 1991, Scottsdale, Arizona.

2. Session Chair, 38th Annual Meeting of the American Society for Artificial Internal Organs (ASAIO), May 1992, Nashville, Tennessee.

3. Session Chair, 19th International Symposium on the Controlled Release of Bioactive Materials, Controlled Release Society, July 1992, Orlando, Florida.

4. Session Chair, XI Congress of the International Society for Artificial Cells, Blood Substitutes, and Immobilization Biotechnology, July 24-27, 1994, Boston, Massachusetts.

5. Session Chair, 22nd International Symposium on the Controlled Release of Bioactive Materials, Controlled Release Society, July 31-August 2, 1995, Seattle, Washington.

6. Session Chair. "The 24th International Symposium on Controlled Release of Bioactive Materials, Stockholm, Sweden, June 15-19, 1997.

7. Session Chair, "The second Annual Meeting of the Israeli Chapter of th Controlled Release Society", Oral Protein and Gene Delivery, September 18-19, 1997

8. Session Chair, "25th Int'l Symposium on Controlled Release of Bioactive Materials", Microparticles Session, June 20-26, 1998.

9. Session Chair, "45th Anniversary Conference of ASAIO" Trends/Developments in Drug Delivery, June 3-5, 1999, San Diego, CA.

10. Session Chair, CRS 2000, July 7-15, 2000, Paris, France.

11. Session Chair, MRS, Nov.27-29, 2000, Boston, MA.

12. Science chair persons (with two other members) for the Bioactive Sessions for the 32nd Annual Conference of the Controlled Release Society to be held in Miami from June 12 -18, 2005.

**University Services**

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| 2002-present | Awards@Benefits committee |
| 1995-present | Biophysics Concentrator |
| 2000-2002 | Brown's Goldwater Scholarship Screening Committee |
| 1991-present | Director of Graduate Students, ABC Section |
| 1993 | Member of Search Committee for new professor in Pharmacology |
| 1994 | Advisor for Sophomore Undergraduates |
| 1995 | Member of Search Committee for new professor in Pharmacology |
| 1995 | Member of the Materials Research Council |
| 1995 - present | Biophysics Concentrator |
| 1996 - present | Hillel Advisor |

**Editorial Activities**

- Member of the Controlled Release Society 1996 Kyoto Scientific Programming and Abstract Review Committee
- Member of the Editorial Board of the *Journal of Biomaterials* 1996-2003
- Member of the Editorial Board of the *Journal of Controlled Release* 1999-2003
- Member of the Editorial Board of the *Journal of microencapsulation*-2000-2003
- Guest Editor for special issue on Drug Delivery Systems for *Journal of Reactive Polymers*
- Editing a book on bioadhesion 1999
- Editing the Encyclopedia of Controlled Drug Delivery Systems 1999
- Scientific Program and Abstract Review Committee Member for the Controlled Release Society, Inc.
- Member of the Editorial Board of *Microencapsulation*, 1998
- Review papers and books for the following Journals:

1. *Journal of Controlled Release*
2. *Biomaterials*
3. *Journal of Polymers Science, Polymer Chemistry*
4. *Pharmaceutical Research*
5. *Biotechnology and Bioengineering*
6. *American Institute of Chemical Engineering*
7. *Journal of Physical Chemistry*
8. *Journal of Pharmaceutics and Biopharmaceutics*
9. *Nature Biotechnology*
10. *Macromolecules*
11. *Nature Medicine*
12. *ASME Journal*
13. *Microencapsulation*
14. *Jacs*

**Other Activities:**

Elected for the Board of Governors of the Controlled Release Society 1997-2001.

National Institute of Health
1. Consultant to NIH Study Section on "Angiogenesis and Breast Cancer", 1994.
2. Peer review of grant application for the National Heart, Lung and Blood Institute, 1995.
3. Special Study Sections of the National Institute of Diabetes and Digestive and Kidney Diseases: SBIR, March 1995.
4. Special Study Section Meeting: Scientific Review, SBIR, Diabetes and Digestive and Kidney Diseases, July 1995.
5. Special Study Section Meeting: Review of grant applications, Nov. 18-19, 1997
6. Panel of chemistry & related sciences, March 11-12, 1998

7. Special Study Section Meeting: Review of small business applications for drug Development and delivery, March 10-11, 1999
8. SB Study Section-Review of applications, June 13-15, 1999.
9. Biodefense, partnerships: vaccines,adjuvants, therapeutics, diagnostics, and resources.2003/05 council ZA/1 HSD-M M3, 04/28/2003.

**List of Publications**

1. E. Mathiowitz, "Release of the contents of microcapsules through controlled rupture by a photochemical method," M.Sc. thesis, (1979), The Weizmann Institute of Science, Israel.

2. E. Mathiowitz, A. Raziel, M.D., Cohen, and E. Fischer, "Photochemical rupture of capsules, I. A model system," *Journal of Applied Polymer Science,* 26, 809-822 (1981).

3. E. Mathiowitz, "Controlled photochemical rupture of capsules," Ph.D. thesis, (1984), The Weizmann Institute of Science, Israel.

4. K. Leong, J. Kost, E. Mathiowitz, and R. Langer, "Polyanhydrides for controlled release of bioactive agents," *Biomaterials,* 7, 364-371 (1986).

5. E. Mathiowitz and R. Langer, "Polyanhydride microspheres as drug carriers. I. Hot melt microencapsulation." *Journal of Controlled Release,* 5, 13-22 (1987).

6. E. Mathiowitz, M.D. Cohen, and R. Langer, "Novel microcapsules for delivery systems," *Reactive Polymers,* 6, 275-283 (1987).

7. F.F. Ghodsian, L. Brown, E. Mathiowitz, D. Brandensburg, and R. Langer, "Enzymatically controlled drug delivery," *Proc. Nat. Acad. Sciences*, USA, 85, 2403-2406, (1988).

8. E. Mathiowitz, W.M. Saltzman, A. Domb, Ph. Dor, and R. Langer, "Polyanhydride microspheres as drug carriers. II. Microencapsulation by solvent removal," *Journal of Applied Polymer Science,* 35, 755-774 (1988).

9. E. Mathiowitz and M.D. Cohen, "Polyamide microcapsules for controlled release, I. Characterization of the membranes," *Journal of Membrane Science,* 40, 1-26 (1989).

10. E. Mathiowitz and M.D. Cohen, "Polyamide microcapsules for controlled release, II. Release characteristics of the microcapsules," *Journal of Membrane Science*, 40, 27-41 (1989).

11. E. Mathiowitz and M.D. Cohen, "Polyamide microcapsules for controlled release, III. Spontaneous release of azobenzene," *Journal of Membrane Science,* Vol. 40, 43-54. (1989).

12. E. Mathiowitz and M.D. Cohen, "Polyamide microcapsules for controlled release, IV. Effects of swelling," *Journal of Membrane Science*, 40, 55-65 (1989).

13. E. Mathiowitz and M.D. Cohen, "Polyamide microcapsules for controlled release, V. Photochemical release," *Journal of Membrane Science*, 40, 67-86 (1989).

14. C. Bindschaedler, K. Leong, E. Mathiowitz, and R. Langer. "Polyanhydride microspheres formulation by solvent extraction," *J. Pharm. Sci,* 77, No. 8, 696-698, (1989).

15. M. A. Howard III, A. Gross, M. S. Grady, R. Langer, E. Mathiowitz, H.R.Winn, M. R. Mayberg, "Intracerebral drug delivery in rats reverses lesion-induced memory deficits," *J. of Neurosurgery,* 71, 105-112, (1989).

16. E. Mathiowitz, Ph. Dor, C. Amato and R. Langer. "Polyanhydride microspheres as drug carriers. III Morphological characterization of microspheres by solvent removal," *Polymer,* 31, 547-555, 1990.

17. E. Mathiowitz, E. Ron, G. Mathiowitz and R. Langer, "Morphological characterization of bioerodible polymers. I. Crystallinity of polyanhydride copolymers." *Macromolecules.* 23, 3212-3218, 1990.

18. E. Mathiowitz, D Kline and R. Langer. "Morphology of polyanhydride microsphere delivery systems," *J. of Scanning Microscopy,* 4, 329-340, 1990.

19. M. Chaisin, E. Ron, E. Mathiowitz, K. Leong, C. Laurencin, H. Brem, B. Grossman and R. Langer. "Polyanhydrides as drug delivery systems," in <u>Biodegradable Polymers as Drug Delivery Systems</u>. Eds., R. Langer and M. Chasin, (Marcel Dekker Inc., NY), pp.43-70, 1990.

20. E. Ron, E. Mathiowitz, G. Mathiowitz and R. Langer," NMR characterization of erodible copolymers." *Macromolecules,* 24, 2278-2282, 1991.

21. E. Mathiowitz and R. Langer., "Polyanhydride microspheres as drug delivery systems," in <u>Microcapsules in Medicine and Pharmacy</u>, (M. Donbrow, ed), CRC, NY, p. 99-123, 1991.

22. Domb, E. Mathiowitz, E. Ron, S., Giannos and R. Langer, "Polyanhydrides IV. Unsaturated and crosslinked polyanhydrides," *Journal of Polymer Science,* 29, 571-579, 1991.

23. Staubli, E. Mathiowitz and R. Langer, "Characterization of hydrolytically degradable amino acid-containing poly(anhydride-co-imides)," *Macromolecules,* 24, 2283-2290, 1991.

24. Staubli, E. Mathiowitz and R. Langer, "Sequence distribution and its effect on glass transition temperatures of poly(anhydride-co-imides) containing asymmetric monomers," *Macromolecules,* 24, 2291-2298, 1991.

25. G. Mikos, E. Mathiowitz, R. Langer and N. Peppas, "The interaction of polymer microspheres with mucin gels as a means of characterizing polymer retention on mucous," *J. of Colloid and Interface Science*, 143, 366-373, 1991.

26. E. Edelman, E. Mathiowitz, R. Langer and M. Klagsbrum, "Controlled and modulated release of fibroblast growth factor," *Biomaterials*, 12, 619-626, 1991.

27. H. Bhagate, R. Mendes, E. Mathiowitz, H. Bhargava, . "A novel, self-correcting membrane coating technique," *Pharmaceutical Research*, vol. 8, 576-583, 1991.

28. E. Mathiowitz, H. Bernstein, Ph. Dor, T. Turek and R. Langer. "Polyanhydride microspheres as drug carriers. IV morphological characterization of microspheres by spray drying," *J. of Applied Polymer Science*, 45, 125-134, 1992.

29. D. Chickering, J.S. Jacob, A. Keung, T.A. Desai and E. Mathiowitz. "Attachment of Mucin Specific Lectins to Alginate for Use as Bioadhesives," *Proceedings of the Materials Research Society Fall Meeting: Biomaterials for Drug and Cell Delivery*, 1993, 331, pp. 67-71.

30. E. Mathiowitz, M. Kreitz and K. Pekarek. "Morphological characterization of bioerodible polymers. 2. Characterization of polyanhydrides by FTIR," *Macromolecules*, 26, 6749-6755, 1994.

31. E. Mathiowitz, J. Jacob, K. Pekarek and D. Chickering, "Morphological characterization of bioerodible polymers. 3. Characterization of the erosion and intact zones in polyanhydrides using scanning electron microscopy," *Macromolecules*, 26, 6756-6765, 1994.

32. Pekarek, J. Jacob and E. Mathiowitz "Double-walled Microspheres for Controlled Drug Release," *Nature*, 367, 258-260, January 20, 1994.

33. K. Pekarek, J. Jacob and E. Mathiowitz "One-step preparation of double-walled microspheres," *Advanced Materials*, 6, No. 9, 684-687, 1994.

34. D. Chickering, J. Jacob, and E. Mathiowitz. "Bioadhesive microspheres: II. Characterization and evaluation of bioadhesion involving hard, bioerodible polymers and soft tissue," *Reactive Polymers*, 25, 189-206, 1995.

35. D. Chickering, and E. Mathiowitz. "Bioadhesive microspheres: I. A Novel electrobalance-based method to study adhesive interactions between individual microspheres and intestinal mucosa," *J. Controlled Release*, 34, 251-261, 1995.

36. D. Chickering, W. P. Harris and E. Mathiowitz, "A Micro-Tensiometer for the Analysis of Bioadhesive Microspheres," *Bioinstrumentation and Technology,* Nov/Dec 501-512, 1995. This paper was the winner of the 1995 Spacelabs Medical Inc./AAMI Annual Meeting Research Manuscript Award.

37. D. Chickering, J. Jacob and E. Mathiowitz, "Poly(Fumaric-co-Sebacic) Microspheres as Oral Drug Delivery Systems, "*Biotechnology and Bioengineering*, 52, 96-101, 1996.

38. K. Pekarek, M. Dyrud, K. Ferrer, Y. Jong, E. Mathiowitz, "In Vitro and *In Vivo* Degradation of Double-Walled Polymer Microspheres," *J. Controlled Release*, 40, 169-178, 1996.

39. Y. Jong, J. Jacob, K. Yip, G. Gardner, E. Seitelman, M. Whitney, S. Montgomery, and E. Mathiowitz, "Controlled Release of Plasmid DNA," *J. Controlled Release,* In press, 1997.

40. D. Chickering, J. Jacob, T. Desai, M. Harrison, W. Harris, C. Morrell, P. Chaturvedi and E. Mathiowitz. "Bioadhesive Microspheres: III. An *In Vivo* Transit and Bioavailability Study of Drug-Loaded Alginate and Poly (Fumaric-co-Sebacic Anhydride) Microspheres," *J. Controlled Release,* vol.48 p 1-8, 1997.

41. M. Kreitz, W. Webber, P.M.Galletti, and E. Mathiowitz, "Controlled Delivery of Therapeutics from Microporous Membranes I. Fabrication and Characterization of Microporous Polyurethane Membranes Containing Polymeric Microspheres," *Biomaterials* 18, 597-603, 1997.

42. E. Mathiowitz, J. Jacob, Y. Jong, G. Carino, D. Chickering, P. Chaturvedi, C. Santos, K. Vijayaraghavan, S. Montgomery, M. Bassett and C. Morrell, "Biologically Erodable Microspheres as Potential Oral Drug Delivery Systems," *Nature* 386, 410-414, 1997.

43. Y. Jong, J. Jacob, K. Yip, G. Gardner, E. Seitelman, M. Whitney, S. Montgomery, and E. Mathiowitz, "Controlled Release of Plasmid DNA," *J. of Controlled Releasee* 47, 123-134, 1997.

44. K. Pekarek Leach, K. Noh, and E. Mathiowitz, "Effects of Manufacturing Conditions of the Formation of Double-walled Polymer Microspheres," *Microencapsulation*, 16, 2 153-167, 1999

45. K. Pekarek Leach, and E. Mathiowitz," Degradation of Double-walled Polymer Microspheres of PLLA and P(CPP:SA) 20:80.I.*In vitro* Degradation", *Biomaterials*, 19, 1973-1980, 1998

46. K. Pekarek Leach, S.Takahashi, and E. Mathiowitz, "Degradation of Double-walled Polymer Microspheres of PLLA and P(CPP:SA)20:80.II *In Vivo* degradation" *Biomaterials*, 19, 1981-1988, 1998

47. W. Webber, F. Lago, and E. Mathiowitz, "Characterization of Soluble Salt Loaded Degradable PLA/PG Films and Their Release of Tetracycline," *Biomedical Materials Research*, 41, 18-29, 1998

48. M.Kreitz, J.Domm, and E.Mathiowitz, "Controlled delivery of therapeutics from microporous membranes.II. *In Vitro* degradation and release of heparin-loaded poly(D, L-lactide-co-glycolide)"Biomaterials, 18 1645-1651, 1997

49. N.Egilmez, Y.Jong, J.Jacobs, C.Santos, E.Mathiowitz, Y.Iwanuma, R.Bankert, "Cytokine immunotherapy of cancer with controlled release biodegradable microspheres in a human tumor xenograft/SCID mouse model, *Cancer Immunology Immunotherapy*, accepted 1998

50. C.Santos, B.Freedman, K.Leach, D.Press, M.Scarpulla, E.Mathiowitz, "Polytumaric-co-sebacic anhydride:A Degradation Study as Evaluated by FTIR, DSC, GPC, and X-ray Diffraction". *Journal of Controlled Release*, 60 (1), 11-22, 1999

51. Y.Jong, N.Egilmez, F-A.Chen, J.Jacob, L.Smith, T.Mottl, R.Bankert, E, Mathiowitz, "Evaluation of cytokine delivery systems for cancer immunotherapy", *Proceedings of the Material Research Society*, accepted 1999

52. N.Egilmez, Y.Jong, F-A.Chen, J.Jacob, E.Mathiowitz, R.Bankert, "Cytokines delivered by biodegradable microspheres promote effective suppression of human tumors by human peripheral blood lymphocytes in the SCID/WINN model", *Journal of Immunology*, accepted 1999.

53. M.Kuriakose, F-A.Chen, N.Egilmez, Y.Jong, E.Mathiowitz, M.Delacure, "W.Hicks, T.Loree, R.Bankert, Interleuckin-12 delivered by biodegradable microspheres promotes the antitumor activity of human peripheral blood lymphocytes in a human head and neck tumor xenograft/SCID mouse model", *Head and Neck*, accepted 1999

54. G.Moodie, D.Ferris, B.Hertzog, C.Chen, E.Mathiowitz, R.Valentini, "Early osteoblast attachment, spreading, and focal adhesion on RGD coated surfaces"*Materials Research Society Symposium Proceedings*, 1999 In Press

55. E.Mathiowitz, D.Chickering, C-M Lehr, editors "Bioadhesive Drug Delivery Systems Fundamentals, Novel Approaches & Development" Marcel Dekker, Inc, 1999

56. E.Mathiowitz, editor "Encyclopedia of Controlled Drug Delivery" vol 1&11, John Wiley pub.1999

57. D.Chickering, C.Santos, E.Mathiowitz, "Adaption of a Microbalance to Measure Bioadhesive Properties of Microspheres", *Bioadhesive Drug Delivery Systems*, 131-146,1999.

58. D.Chickering, E.Mathiowitz, "Definitions, Mechanisms, and Theories of Bioadhesion", *Bioadhesive Drug Delivery Systems*, 1999 p 1-10.

59. B.Hertzog, E.Mathiowitz, "Novel Magnetic Technique to Measure Bioadhesion" *Bioadhesive Drug Delivery Systems*, 1999

60. G.Carino, J.Jacobs, C.J.Chen, C.Santos, B.Hertzog, E.Mathiowitz, "Bioadhesive, Bioerodible Polymers for Increased Intestinal Uptake" *Bioadhesive Drug Delivery Systems*, 1999

61. E.Mathiowitz, M.Kreitz, "Microencapsulatiion" *Encyclopedia of Controlled Drug Delivery*, 1999

62. E.Mathiowitz, D.Chickering, J.Jacob, C.Santos, "Bioadhesive Drug Delivery Systems" *Encyclopedia of Controlled Drug Delivery*, 1999

63. C.A.Santos, J.S.Jacob, B.A.Hertzog, B.D.Freedman, D.L.Press, P.Harnipicharnchai, E.Mathiowitz, "Correlation of two Bioadhesion assays: the everted sac technique and the CAHN Microbalance" *Journal of Controlled Release*, 1999

64. G.Carino, E.Mathiowitz, "Oral Insulin Delivery" *Advanced Drug Delivery Reviews*, 1999

65. B A Hertzog, CA Santos, P May, E Mathiowitz, "Tensile Testing of AxyaLoop™ Ultrasonically Welded Suture in Ligament Repair" *Axya Medical*, 1999

66. E. Mathiowitz, J. Jacob, Y. jong, T. M. Henkal, W. S. Spano, R. Guemonprez, A.M. Klibanov. R. Langer."Novel deciccants Based on Designed Polymeric Blends"J. *Applied Polymer Science*, 80,317-327,2001.

67. N.Egilmez, Y.Jong, M.Sabel, J.Jacob, E.Mathioiwitz, R.Bankert, "*In Situ* Tumor Vaccination with Interleukin-12-encapsulated Biodegradable Microspheres:Induction of Tunor Regression and Patent Antitumor Immunity", Cancer Research 60, 3832-3837, July, 2000

68. M.Sandor, P.D Enscore, Weston, E.Mathiowitz, "Effect of protein molecular weight on release from micron-sized PLGA microspheres *Journal of Controlled Release* 7, 297-311, 2001

69. M.Sandor, NA Bailey, E Mathiowitz "Characterization of polyanhydride microsphere degradation by DSC," *Polymers*, 43/2, pp279-288, 2001

70. E Mathiowitz, JS Jacob, YS Jong, TM Hekal, W Spano, R Guemonprez, AM Klibanov, R Langer, "Novel Desiccants Based on Designed Polymeric Blends", *Journal of Applied Polymer Science*, 80, 317-327, 2001

71. M. Sandor, A Riechel, I Kaplan, E Mathiowitz, "Effect of Lecithin and $MgCO_3$ as additives on the enzymatic activity of carbonic anhydrase encapsulated in PLGA microspheres" *Biochemica et Biophysica Acta*,1570,1, 69-74.2002

72. J Godbee, P Weston, E Mathiowitz, "The effects of infiltration on protein release from multi-phase microspheres fabricated via solvent removal" accepted by *Journal of Microencapsulation*, 19,783-796, 2002.

73. NA Bailey, M Sandor, M Kreitz, E Mathiowitz, "Comparison of the Enthalpic Relaxation of Poly(Lactide-Co-Glycolide) 50:50 Nanospheres and Raw Polymer" *J Applied Polymer Science*, 86,1868-1872, 2002.

74. M. Sandor, J Harris, E Mathiowitz, "A Novel Polyethylene Depot Device for the Study of PLGA Microspheres *in Vitro* and *in Vivo*" *Biomaterials*, 23,4413-4423, 2002.

75. M. Sandor, S Mehta, J Harris, C Thanos, J Marshall, P Weston "Transfection of HEK Cells via DNA-leaded PLGA and P(FASA)" *J Drug Targeting*, 10, 497-506, 2002.

76. CA Santos, BD Freedman, S Ghosn, JS Jacob, M Scarpulla, DJ Enscore, E Mathiowitz, "Effect of Polyanhudride Microsphere Composition on Bioadhesion. Evaluation of anhydride oligomers" *Biomaterials*, 24,3571-3583,2003

77. CG Thanos, Z Liu, J Reineke, E Edwards, E Mathiowitz, "Improving the Bioavailability of the Poorly-Soluble Drug Dicumarol by using Micronization and the Formation of a Solid Solution" In press *Pharm Res*, 2002

78. CG Thanos, Z Liu, YS Yong, JS Jacob, M Sandor, E Edwards, E Mathiowitz. "Improving the Oral Bioavailability of Poorly Soluble Drugs: The Effects of Formulating Dicumarol with a Bioadhesive Polyanhydride in the Rat", *Pharmaceutical research* accepted March 31.

79. CG Thanos, Z Liu, M Goddard, J Reineke, N Bailey, M Cross, R Burrill,, E Mathiowitz, "Enhancing the Oral Bioavailabliity of the Poorly Soluble Drug

Dicumarol with a Bioadhesive Polymer" Accepted March 31, *J Pharm Sci*, 2002

80. Hess SD, Egilmez NK, Bailey N, Anderson TM, Mathiowitz E, Bernstein SH,Bankert RB."Human CD4+ T cells present within the microenvironment of human lung tumors are mobilized by the local and sustained release of IL-12 to kill tumors in situ by indirect effects of IFN-gamma." *J. Immunol.* Jan 1;170(1):400-412, 2003.

81. E, Mthiowitz and J. Jacob. " a Novel Mechanism for spontaneous encapsulation of active agents: Phase Inversion Nanoencapsulation. Chapter in ACS book. In press.

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85. Ferris, D.M. and Mathiowitz, E. Directed endothelial and progenitor cell proliferation, orientation and migration through sustained release of rhVEGF165 *in vitro* and *in vivo*. Podium presentation, 30th Annual Meeting of the Controlled Release Society, Glasgow, Scotland, United Kingdom, July 19-23, 2003.

86. Stacia Furtado, Emily Bubbers, Paula Weston, Haitao Qian, Roxanne Burrill, Jules Jacob and Edith Mathiowitz. Oral Delivery of Insulin Using Bioadhesive Microspheres. Glasgow, Scotland, United Kingdom, July 19-23, 2003.

87. Joshua Reineke, Christopher Thanos, Stephen Chen and Edith Mathiowitz. Enhanced Oral Delivery of Hydrophobic Drugs Encapsulated by Poly [Fumaric-co-Sebacic] Anhydride Department of Molecular Pharmacology, Physiology and Biotechnology
Brown University, Providence, RI USA 2004.

**Invited lectures**

1. "Novel microcapsules for delivery systems" at Eastman Kodak, Rochester, NY, summer 1985.

2. "Polymeric drug composites: Structure-property relationships for novel delivery systems", Dept. of Material Sciences, MIT, March 1987.

3. "Photochemically controlled delivery systems", Du Pont & Co., R&D Division, Wilmington, Delaware, 1987.

4. "Structure property relationships for novel polymeric delivery systems". Department of Pharmaceutical Chemistry School of Pharmacy, University of California, San Francisco, April 8, 1988.

5. "Morphological characterization of microparticles". Presented in a course on microencapsulation. "Microencapsulation and Nanoencapsulation - process and Pharmaceutical Applications", Sponsored by the Controlled Release Society, Boston, May 14-15, 1990.

6. "Microencapsulation and drug delivery" Panel Chairman, annual Meeting of the society for Biomaterials, Scottsdale, Arizona, May 1991.

7. "Morphological characterization of biomaterials using X-Ray, DSC and SEM." Eastern Analytical Symposium, Inc., Somerset, NJ, November 1991.

8. "Evaluation and characterization of composite drug delivery systems." American Chemical Society (ACS) meeting, San Francisco, CA, April 1992.

9. "Bioadhesive microspheres as drug delivery systems" Invited lecture at the 38th Annual meeting of the American Society for Artificial Internal Organs (ASAIO), Nashville, TN, May 1992.

10. "Mechanism study on the interaction of bioadhesive microspheres with intestinal mucosa." Invited lecture at the Surface of Biomaterials Symposium, Minneapolis, MN, October 1992.

11. "Drug delivery systems" Panel Chairman, Annual Meeting at the 39th Annual meeting of the American Society of Artificial Internal Organs (ASAIO), New Orleans, LA, May 1993.

12. "Microspheres as drug delivery systems." Invited lecture at the Surgical Research Seminar, The Miriam Hospital, Department of Surgery, Providence, RI, September, 1992.

13. "The mechanism of bioadhesion between hydrogels, thermoplastics and intestinal mucosa." Invited lecture at the PPST Research Seminar, Departments of Chemical Engineering and of Material Science at the Massachusetts Institute of Technology, Cambridge. MA, October 1992.

14. "Controlled and Sustained Release Formulations Designed for Protein Drugs Pt. I & II. Speaker in short course "Formulation Development of Therapeutic Proteins and Drug Delivery Systems for Peptide and Protein Drugs," American Chemical Society Short Course, Chicago, IL, 1992-present.

15. "Drug delivery systems." Invited lecture at Morehouse College, Atlanta, Georgia, February 25, 1993.

16. "Mucus Epithelia." Invited lecture at the Keystone Symposia Conference, Hilton Head Island, South Carolina, January 7-13, 1994.

17. "Novel Double-Walled Microspheres For Oral Or Parental Administration." Invited lecture at XI Congress of the International Society For Artificial Cells, Blood

Substitutes, and Immobilization Biotechnology, Boston, Massachusetts, July 24-27, 1994.

18. "Bioadhesive microspheres as drug delivery systems." Invited lecture at Alza, Palo Alto, California, September 8, 1994.

19. "Bioadhesive microspheres as drug delivery systems." Invited lecture at Cygnus Therapeutics Systems, Redwood City, California, September 9, 1994.

20. "The Proprietary Dilemma - Bridging the Information Gap Between Academia and Practice," Annual Congress of the Association of Faculties of Pharmacy of Canada, Montreal, Canada, May 11, 1995.

21. "Bioadhesive Drug Delivery Systems". Invited lecture at Engineering Foundation Conference, BIOCHEMICAL ENGINEERING IX: Interdisciplinary Foundations for Creating New Biotechnology, in Davos, Switzerland, May 21-26, 1995.

22. "Hydrophobic Polymer Microspheres for Oral Delivery of DNA, Proteins, Peptides, and Small Molecules in the Small Intestine." Invited lecture at VRI Virus Research Institute, 61 Moulton Street, Cambridge, MA 02138 April 1997.

23. "Hydrophobic Polymer Microspheres for Oral Delivery of DNA, Proteins, Peptides, and Small Molecules in the Small Intestine." Invited lecture at Eli Lilly and Co., Indianapolis, IN, May 8, 1997.

24. "Hydrophobic Polymer Microspheres for Oral Delivery of DNA, Proteins Peptides", Ares Services, 15 bis, Ch. des Mines, CH-1202 Geneva, Switzerland, June 1997.

25. "Hydrophobic Polymer Microspheres for Oral Delivery of DNA, Proteins Peptides" Amgen Corporation, 1900 Oak Terrace Lane, Thousand Oaks, CA 91320, July 1997.

26. "Bioadhesive Polymers as Oral delivery Systems", Affymax Research Institute, 3410 Central Expressway, Santa Clara, California 95051, July, 1997.

27. "Hydrophobic Polymer Microspheres for Oral Delivery of DNA, Proteins Peptides", Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O.Box 191, New Brunswick, NJ 08903-0191, July 1997.

28. "New Opportunities in Drug Delivery Systems", Corporate Research and Technology, Hoechst Celanese Corporation, R.L. Mitchell Technical Center, 86 Morris Avenue, Summit, NJ 07901 July 1997.

29. "Bioadhesive Microspheres as Oral Delivery Systems for Proteins and Genes" Enzon, Inc. Piscutway, NJ, August 1997.

30. "Bioadhesive Microspheres as Oral Delivery Systems for Proteins and Genes", the 4th US-Japan Symposium on Drug Delivery Systems, Kauai, Hawaii, December, 1997.

31. "Characterization of Drug Delivery Polymers using DSC and FT-IR" Thermal Analysis Fall Seminar Series, Westborough Marriottt, 5400 Computer Drive, Westborough, MA, November, 1997.

32. "Bioadhesive Polymers for Oral DNA Delivery", Keystone Symposia, Silverthorne, CO, January 1998.

33. "Bioadhesive Polymers for Oral DNA Delivery", Roswell Park Cancer Cancer Center, Buffalo, NY, Jan.27, 1998.

34. "Drug Carriers in Biology and Medicine", Gordon Research Conference, Ventura, CA. February, 1998.

35. "Bioadhesive Microspheres as Oral Delivery Systems for Proteins and Genes", Micrologix Biotech, Inc. Vancouver, B.C. February, 1998

36. "Drug Carriers in Biology and Medicine", UCSF, Dept.of Pharmaceutical Chemistry, San Francisco, CA. March 1998.

37. "Development of Oral Delivery of Proteins and Genes", 9th Int'l Symposium on Recent Advances in Drug Delivery Systems, Feb.22-25, 1999.

38. "Oral Delivery of Protein and Genes:Realty or Myth?", CRS Annual Meeting, Boston, MA, June 24, 1999.

39. "Bioavailability Testing of Insulin-Loaded Microspheres", "The Effect of Protein Molecular Weight on Release from PLGA Nanospheres", "Solvent Removal for Protein Encapsulation", "Biodegradable Nanosphere Uptake in the Rabbit Jejunum", New England Pharmacy Conference, Providence, RI, Feb, 2000.

88. "Enhanced Oral Delivery of Macromolecules using Bioadhesive Microspheres". AAPS Pharmaceutics and Drug Delivery Conference. April 22-24, 2002, Arlington, VA, USA, 2002.

40. Mechanism for Spontaneous Encapsulation of Active Agents: Phase Inversion NanoencapsulationThe ACS Division of Colloid and Surface Science,Colloidal Drug Delivery,Co-sponsored by American Association of Pharmaceutical svience (APPS). Orlando, FL, April 7-11, 2002

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(54) **Controlled absorption diltiazem formulations**

(57) A controlled absorption diltiazem pellet formulation for oral administration comprises a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, and a multi-layer membrane surrounding the core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble synthetic polymer. The number of layers in the membrane and the ratio of the water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of diltiazem from the pellet at a rate allowing controlled absorption thereof over not less than a twelve hour period following oral administration. The pellet has a dissolution rate in vitro which when measured in a dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 results in not more than 35% of the total diltiazem being released after 2 hours of measurement. Not more than 60% of the total diltiazem is released after four hours of measurement and 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

EP 0 856 313 A1

**Description**

This invention relates to controlled absorption pharmaceutical formulations and, in particular, to controlled absorption forms of diltiazem for oral administration.

Diltiazem-cis-(+)-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one, is a benzothiazine derivative possessing calcium antagonist activity. Diltiazem blocks the influx of calcium ions in smooth and cardiac muscle and thus exerts potent cardio-vascular effects. Diltiazem has been shown to be useful in alleviating symptoms of chronic heart disease, particularly angina pectoris and myocardial ischemia and hypertension, while displaying a low incidence of side effects. Diltiazem is conventionally administered in tablet form (30 mg or 60 mg) as diltiazem hydrochloride sold under the Trade Mark Cardizem (Marion Laboratories Inc.). Diltiazem in tablet form (30 mg) is also sold under the Trade Mark Herbesser (Tanabe Seiyaku). Diltiazem is also sold in capsule form.

Conventional diltiazem therapy starts with 30 mg adminstered 4 times daily. The dosage is gradually increased to 240 mg, given in divided doses three or four times daily, at one- to two- day intervals until an optimum response is obtained. Diltiazem is extensively metabolized by the liver and excreted by the kidneys in bile. According to professional use information issued by Marion Laboratories Inc., Cardizem is absorbed from the known tablet formulation to about 80% and is subject to an extensive first-pass effect, giving an absolute bioavailability, compared to intravenous administration, of about 40%. Single oral doses of 30 to 120 mg of Cardizem result in peak plasma levels 2-3 hours after administration. Detectable plasma levels occur within 30-60 minutes after administration indicating that Cardizem is readily absorbed.

The plasma elimination half-life following single or multiple administration is approximately 3-5 hours. Therapeutic blood levels of Cardizem are thought to be in the range of 50-200 ng/ml.

As stated above, conventional diltiazem capsules and tablets are administered three or four times daily. Such frequent drug administration may reduce patient compliance and produces irregular blood levels; thus adverse therapeutic effects can arise.

An article by McAuley, Bruce J. and Schroeder, John S. in Pharmacotherapy 2: 121, 1982 states that peak plasma levels of diltiazem occur within one hour with normal capsules and within 3 to 4 hours with sustained release tablets. However, the Applicants have found that peak plasma levels of diltiazem occurring within 3 to 4 hours following administration were incompatible with effective and efficacious twice-daily administration of diltiazem, and that peak plasma levels occurring within 6 to 9 hours as obtained in the case of the controlled absorption diltiazem formulation of the Applicants' EP-A-0 149 920 satisfy accepted criteria for twice-daily administration of diltiazem, with preferred levels occurring within 8 to 9 hours. Furthermore, it will be appreciated peak plasma levels of diltiazem occurring within 3 to 4 hours are incompatible with effective and efficacious once-daily administration of diltiazem.

The Applicants' EP-A-0 149 920 describes and claims an effective diltiazem formulation for twice-daily administration. The formulation is distinguished by a characteristic dissolution rate when tested under specified conditions, not least its controlled absorption characteristics in vivo, which offer distinct advantages over existing formulations. However, it has been found with certain formulations prepared in accordance with EP-A-0 149 920, when manufactured in production batches commensurate with commercial scale manufacture to the indicated specifications, that the in vitro performance of the formulation disimproved beyond acceptable limits when stored over the normally required shelf-life periods. This was found to be particularly the case with formulations containing the naturally occurring polymer shellac. It is known that such naturally occurring polymers can exhibit considerable variability in quantity and quality depending on the source and time of collection and accordingly there remains a need to produce alternative formulations which do not require their use.

It is an object of the present invention to provide a controlled absorption diltiazem formulation suitable for administration no more frequently on the average than at twelve hour intervals.

It is another object of the present invention to provide a controlled absorption diltiazem formulation suitable for once-daily administration and which is bioequivalent to known oral formulations of diltiazem.

It is another object of the present invention to provide a controlled absorption diltiazem formulation suitable for once- and twice-daily administration, which is bioequivalent to known oral formulations of diltiazem, which has good stability over normal shelf-life periods of eighteen months to two years, and which contains only synthetic polymeric materials.

A further object of the present invention is to improve the method of manufacture of said formulations.

Another object of the present invention is to provide a controlled absorption diltiazem formulation which is particularly effective when administered at specific times during the day.

Accordingly, the invention provides a controlled absorption diltiazem pellet formulation for oral administration, said pellet comprising a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, the diltiazem component and the organic acid being present in a ratio of from 50:1 to 1:1, and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble syn-

thetic polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said diltiazem from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a twelve hour period following oral administration, said rate being measured in vitro as a dissolution rate of said pellet, which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) no more than 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) no more than 60% of the total diltiazem is released after 4 hours of measurement in said apparatus; and
c) 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

It will be appreciated that, when a once-daily formulation of the present invention is given prior to bedtime, it may be desirable to administer a formulation having a slower initial release during the night followed by an increased rate of release occurring in the morning as the patient awakens and commences activity.

Therefore, it may be desirable to administer a formulation which is effective for once-daily administration wherein the in vitro dissolution rate has the following pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 0 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 10 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 25% to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

It will also be appreciated that the active ingredients of the present invention are generally given to chronically ill patients wherein a steady state equilibrium is reached after several days or so of treatment. Patients that have achieved steady state are less susceptible to fluctuations ordinarily observed following administration of a single dose.

Those skilled in the art will appreciate that depending on the time of administration throughout the day and the preferred bioprofile to be achieved, products may be formulated with dissolution profiles falling within various subdivisions within the foregoing ranges. A particularly preferred once-daily product normally to be administered prior to bedtime or in the morning upon awakening would be formulated to achieve the following dissolution profile:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 5 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

The time of administration discussed above for once-daily administration of drugs is also applicable to twice-daily formulations. Those skilled in the art will appreciate that twice-daily products may be formulated within selected subdivisions depending on the preferred time of administration.

The invention thus further provides a diltiazem pellet formulation according to the above which is effective for twice-daily administration wherein the in vitro dissolution rate has the following pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 35 to 85% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) 100% of the total diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

A particularly preferred diltiazem formulation which is effective for twice-daily administration is one wherein the in vitro dissolution rate has the following pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 55 to 80% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

Whereas the formulation of EP-A-0 149 920 is eminently suitable for twice-daily administration of diltiazem, the Applicants have found in the case of the present invention that peak plasma levels of 10 to 19 hours are essential in satisfying accepted criteria for once-daily administration of diltiazem, with preferred levels occurring within 12-14 hours. The present invention achieves this extension in time to peak plasma level as defined herein by tmax.

The invention also provides a controlled absorption diltiazem formulation for once-daily oral administration, comprising pellets as hereinbefore defined, said formulation including a sufficient quantity of a rapid release form of diltiazem so as to have a dissolution rate which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 10 to 60% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 90% of the total diltiazem is released after a total of 8 hours of measurement in said apparatus;
d) from 60 to 100% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

Preferably, the once-daily formulation comprises a blend of pellets as hereinbefore defined together with up to 25% by weight of said rapid release form of diltiazem.

Most preferably, the rapid release form of diltiazem comprises pellets as hereinbefore defined without said membrane.

Preferably, the diltiazem is in the form of a pharmaceutically acceptable salt thereof, more particularly the hydrochloride salt thereof.

The organic acid is preferably represented by one or more of the following acids: adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid. Especially preferred acids are adipic acid, fumaric acid and succinic acid. The diltiazem component and organic acid are preferably present in a ratio of from 10:1 and 2:1, more especially 6:1 to 3:1.

The core also optionally contains a lubricant which is represented by one or more of the following: sodium stearate, magnesium stearate, stearic acid or talc. The diltiazem and lubricant are preferably present in a ratio of from 5:1 to 100:1 for the once-daily formulation. The preferred diltiazem and lubricant ratio for the twice-daily formulation is from 0.5:1 to 45:1.

Preferably, the core comprises diltiazem or a pharmaceutically acceptable salt thereof and the associated organic acid embedded in a polymeric material. The diltiazem component and polymeric material are preferably present in a ratio of from 1:1 to 100:1, more particularly from 5:1 to 30:1. The polymeric material may be rapidly soluble in water or, alternatively, may be freely permeable to diltiazem and water.

Suitably, the core comprises:

a) a powder mixture containing diltiazem or a pharmaceutically acceptable salt thereof, an organic acid selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble synthetic polymer and a minor proportion of a pharmaceutically acceptable water insoluble synthetic polymer,
said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

The term water soluble polymer as used herein includes polymers which are freely permeable to water such as Eudragit RL. Likewise, the term water insoluble polymer as used herein includes polymers which are slightly permeable to water such as Eudragit RS.

The polymeric material preferably consists solely of a water soluble polymer or a polymer which is freely permeable to diltiazem and water. Alternatively, the polymeric material of the core may include a minor proportion of water insoluble polymer or a polymer which is slightly permeable to diltiazem and water. The ratio of water soluble/freely permeable to water insoluble/slightly permeable polymer is determined by the particular combination of polymers selected. However, in the case of a core including a water soluble polymer and a water insoluble polymer, the ratio of water soluble polymer to water insoluble polymer will normally be in the range of 1:1 to 50:1, more especially 3:1 to 9:1.

The water soluble polymer is suitably polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or polyethylene glycol or a mixture thereof. An especially preferred water soluble polymer is polyvinylpyrrolidone.

A suitable polymer which is freely permeable to diltiazem and water is a polymer sold under the Trade Mark EUDRAGIT RL.

The water insoluble polymer is suitably ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate),

poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

A suitable polymer which is slightly permeable to diltiazem and water is a polymer sold under the Trade Mark EUDRAGIT RS or a polymer whose permeability is pH dependent and sold under the Trade Mark EUDRAGIT L, EUDRAGIT S or EUDRAGIT E.

EUDRAGIT polymers are polymeric lacquer substances based on acrylates and/or methacrylates.

Polymeric materials sold under the Trade Marks EUDRAGIT RL and EUDRAGIT RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups and are described in the "EUDRAGIT" brochure of Messrs. Rohm Pharma GmbH (1985) wherein detailed physical-chemical data of these products is given. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT RL and RS are freely permeable (RL) or slightly permeable (RS), respectively, independent of pH.

EUDRAGIT L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of EUDRAGIT L is pH dependent. Above pH 5.0, the polymer becomes increasingly permeable. EUDRAGIT L is described in the "EUDRAGIT L" brochure of Messrs. Rohm Pharma GmbH (1986) wherein detailed physical-chemical data of the product is given.

The core suitably has between 50 and 200 layers of the core-forming materials and is built up in a manner known per se.

Preferably, the multi-layer arrangement of diltiazem, organic acid and polymeric material is built up on a central inert core in a conventional coating pan. The core suitably consists of a non-pareil bead or seed of sugar/starch having an average diameter in the range 0.4-0.8 mm, especially 0.5-0.6 mm for a twice-daily formulation and especially 0.6-0.71 mm for a once-daily formulation. Alternatively, the diltiazem, organic acid and polymeric material may be built up on a central inert core as hereinbefore defined in an automated coating system, for example, a CF granulator.

The core may also include further components to those specified above such as a dispersing agent, glidant and/or surfactant.

The diltiazem, organic acid and optional other components are blended to form a homogenous powder. The blend is suitably passed through an appropriate mesh screen using a milling machine. In the case of coating in a conventional coating pan, alternate layers of a coating solution/suspension of the polymeric material and the powder are applied to the central inert core so as to build up the multi-layer arrangement of the active core.

In the case of an automatic coating system, the coating solution/suspension of the polymeric material and the powder are applied simultaneously, in conventional manner. The coating solution/suspension of the polmeric material comprises one or more polymers dissolved/suspended in a suitable solvent or mixture of solvents. The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension. Preferably, between 10 and 40 parts of inert cores are used relative to the homogenous powder. The addition of a plasticizing agent to the polymeric solution/suspension may be necessary depending on the formulation to improve the elasticity and also the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes could affect the drug release rate. Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides.

Preferred coating materials include - solutions/suspension of the polymers cited for use in the application of the powder blend to the central inert core in a suitable organic/aqueous carrier medium.

As indicated above, the membrane of the film-forming polymer or mixture of polymers surrounding the core preferably has a major proportion of a water insoluble polymer and optionally a minor proportion of a water soluble polymer, the ratio of water insoluble to water soluble polymer (when present) being determined by the inherent solubility characteristics of the polymer selected.

The membrane may also be composed of a proportion of a polymer which is slightly permeable to diltiazem and water and a proportion of a polymer which is freely permeable to diltiazem and water, the ratio of slightly permeable to freely permeable polymer being determined by the inherent permeability of the respective polymers. The terms "water soluble" and "water insoluble" polymer embrace such polymers as indicated above.

A suitable combination of a polymer which is slightly permeable to diltiazem and water and a polymer which is freely permeable to diltiazem and water is EUDRAGIT RS and EUDRAGIT RL in a ratio of from 1:1 to 50:1, especially 2:1 to 10:1. The membrane may also include a combination of water soluble/water insoluble polymers and polymers which are freely permeable/slightly permeable to diltiazem and water.

The membrane may also comprise a mixture of polymers that are water soluble, freely permeable, water insoluble, slightly permeable and polymers whose permeability/solubility is affected by pH.

Especially suitable polymers for the membrane include:

Polyvinylpyrrolidone, ethylcellulose, Eudragit RL, Eudragit L, Eudragit E, Eudragit S, cellulose acetate and polyvinyl alcohol. Commercially available ready-made polymeric solutions/suspensions are also especially preferred. These ready made solutions/suspensions may optionally contain plasticizing agents to improve the polymer film as described previously. Examples of ready-made solutions/suspensions of polymeric material with or without plasticizing agent include Eudragit RL 30D, Eudragit L 30D, Eudragit E 12.5, Eudragit RL 12.5 P, Eudragit RS 12.5, (Eudragit being a Trade Mark of Rohm and Haas, whose technical brochures describe the differences between the products), Aquacoat (a Trade Mark of FMC Corporation) and Sure-lease (a Trade Mark of Colorcon Inc.).

The membrane may be built up by applying a plurality of coats of membrane polymer solution or suspension to the core as hereinafter described. The membrane solution or suspension contains the polymer(s) dissolved or suspended, respectively, in a suitable aqueous or organic solvent or mixture of solvents, optionally in the presence of a lubricant. Suitable lubricants are talc, stearic acid, magnesium stearate and sodium stearate. A particularly preferred lubricant is talc. The membrane, polymer or mixture of polymers may optionally include a plasticizing agent, the function and choice of which has been previously described.

Preferably, the number of coats of membrane solution or suspension applied is between 20 and 600. The dissolution rate achieved is proportionally slower as the number of membrane coats increases.

The membrane solution or suspension may be applied to the active cores in a conventional coating pan as indicated or, alternatively, using an automated system such as a CF granulator, for example a FREUND CF granulator, a GLATT fluidized bed processor, an AEROMATIC, a modified ACCELA-COTA or any other suitably automated bead coating equipment (FREUND, GLATT, AEROMATIC and ACCELA-COTA are all Trade Marks).

Preferably 2-25 ml of membrane solution/suspension is applied per coat per kilogram of active cores. In an automated system the total amount of membrane solution/suspension applied to the active cores is the same as that applied in a conventional coating pan, expect that the membrane solution/suspension is applied continuously.

Preferably, when a coating pan is used the membrane is applied at a rate of 20-30 coats between each drying step until all of the coats have been applied. Between applications the pellets are dried for more than 12 hours at a temperature of 50-60°C, most suitably 55°C.

In an automated system the membrane is preferably applied at a rate which is equivalent to the application of 20-30 coats/day. After each application of this amount of membrane solution/suspension, the pellets are dried at the temperature and for the length of time specified for coating in a coating pan.

In an automated coating system the rate of application of membrane solution/suspension is suitably 0.5-10 g/kg of cores/min. The rate of application of lubricant such as talc is also suitably 0.5-10 g/kg of cores/min.

The pellets may be filled into hard or soft gelatine capsules. The pellets may also be compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the Trade Mark "AVICEL" or a co-crystallised powder of highly modified dextrins (3% by weight) and sucrose sold under the Trade Mark "DI-PAC" in such a way that the specific dissolution rate of the pellets is maintained.

In the management of cardiovascular disorders, it is often beneficial and desirable to target one or more vectors of the intricate internal blood pressure control system in order to achieve maximum therapeutic effect. For example, in addition to blocking the influx of calcium ions it may be desirable to inhibit angiotensin converting enzyme (ACE), the activity of which is known to increase blood pressure by promoting vasoconstriction of the arterioles and sodium retention. To this end, this invention also relates to a pharmaceutical formulation of diltiazem and an ACE-inhibitor in an oral dosage form suitable for concomitant and combined administration providing for controlled release over a 24 hour period when given once or twice daily.

For combined use, the ACE-inhibitor or pharmaceutically acceptable salt thereof and the diltiazem or pharmaceutically acceptable salt thereof as defined herein are contained in a single dosage form to achieve desired plasma profiles for either once-daily or twice-daily administration.

The ACE-inhibitor can be combined with the sustained release diltiazem formulations either as pure active ingredient or active cores produced substantially in the same manner as discussed above for the diltiazem active cores. Both the diltiazem and the ACE-inhibitor may be formulated in the same active core.

For concomitant use, the ACE-inhibitor or pharmaceutically acceptable salt thereof and the diltiazem or pharmaceutically acceptable salt thereof as defined herein are contained in discrete dosage forms to achieve desired plasma profiles for either once-daily or twice-daily administration of the two active ingredients.

In a once-daily formulation, the amount of ACE-inhibitor present is no greater than that amount given as the normal daily dosage. It follows that a twice-daily formulation contains half the amount of ACE-inhibitor given as the normal daily dosage. Normally, the ratio of diltiazem to ACE-inhibitor will be between 50:1 and 1:5, preferably 20:1 to 1:1.

As will be appreciated, however, by those skilled in the art, both drugs exert an effect on the cardiovascular system but through different routes of action. For example, in controlling hypertension, each drug may be used in combination in daily amounts less than that which would be used when each drug is used alone.

Suitable ACE-inhibitors include captopril, fosenopril, enalapril, ramipril, zofenopril, quinapril, cilazapril, spirapril, lisinopril, delapril, pivalopril, fentiapril, indolapril, alacepril, tiapamil (N-(3,4-dimethoxyphenethyl)-3-[2-(3,4-dimethoxyphe-

nyl)-1,3-dithian-2-yl]-N-methylpropylamine 1,1,3,3-tetraoxide), pentopril, rentiapril and perindopril.

Preferred ACE-inhibitors include captopril and enalapril.

According to a further aspect of the invention there is provided use of diltiazem or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control of hypertension and the symptoms of angina over a twenty-four hour period following administration of a single therapeutically effective dose thereof. Furthermore, in accordance with the invention one may administer once-daily in combination or concomitantly with the diltiazem or pharmaceutically acceptable salt thereof a single therapeutically effective dose of an ACE-inhibitor as hereinabove defined.

In the accompanying drawings:

Fig. 1 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 13 (curve a) compared with a diltiazem formulation prepared in accordance with our EP-A-0 149 920 (curve b);

Fig. 2 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 14 (curve a) compared with a diltiazem formulation prepared in accordance with our EP-A-0 149 920 (curve b);

Fig. 3 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 15 (curve a) compared with conventional tablets (curve b);

Fig. 4 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 15, stored under ambient conditions as hereinafter described, and tested at different times after manufacture;

Fig. 5 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 15, 'stored' under accelerated conditions as hereinafter described and tested at different times after manufacture; and

Fig. 6 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 1 of our EP-A-0 149 920 'stored' under accelerated conditions as hereinafter described, and tested at different times after manufacture.

The invention will be further illustrated by the following Examples:-

EXAMPLE 1

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a suitable mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (10 kg) using a FREUND CF granulator and a coating solution of:

9% polyvinylpyrrolidone
in ethanol

A membrane was then applied to the active cores by spraying on a solution consisting of:

| | |
|---|---|
| 12.5% EUDRAGIT RS in acetone/isopropanol 40:60 | 40 parts by weight |
| 12.5% EUDRAGIT RL in acetone/isopropanol 40:60 | 10 parts by weight |
| Isopropanol | 50 parts by weight |

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc was 1:0.62 viz. 0.62 grams of talc is applied per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 50 kg of active cores to achieve the following dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution test. The dissolution rate of the pellets was tested by the method of the U.S. Pharmacopoeia XXI Paddle Method in 0.05 M KCl, at pH 7.0 and at

100 r.p.m.

The diltiazem hydrochloride was quantitively determined using u.v. spectrophotometry at 237 nm. The dissolution rate was as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 2.3 |
| 4 | 17.7 |
| 8 | 49.0 |
| 13 | 76.5 |
| 24 | 95.7 |

EXAMPLE 2

Example 1 was repeated except that the application of membrane-forming suspension was continued until the following dissolution profile was obtained.

The dissolution rate of the pellets so prepared was determined according to the procedure of Example 1 and was found to be as follows:

| Time (hours) | % Diltiazem Hydrochloride release |
|---|---|
| 2 | 0.8 |
| 4 | 13.8 |
| 8 | 52.6 |
| 13 | 80.4 |
| 24 | 98.1 |

EXAMPLE 3

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (10 kg) employing a granulator using a coating solution of:

9% polyvinylpyrrolidone
in ethanol

A membrane was then applied to the active cores by spraying on a solution consisting of:

| | |
|---|---|
| 12.5% EUDRAGIT RS in acetone/isopropanol 40:60 | 41 parts by weight |
| 12.5% EUDRAGIT RL in acetone/isopropanol | 10 parts by weight |
| Isopropanol | 49 parts by weight |

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 1:0.62 viz. 0.62 grams of talc is applied per gram of membrane solution. A sufficient amount of membrane solution (includes solvents) and talc was applied to 50 kg of active cores to achieve a dissolution

rate of the pellets (determined in the manner set out in Example 1) as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 0.7 |
| 4 | 16.8 |
| 8 | 62.9 |
| 13 | 87.6 |
| 24 | 98.7 |

An amount of the sustained release pellets so prepared (85% by weight of active ingredient) was combined with an amount (15% by weight of active ingredient) of immediate release pellets corresponding to active cores without the membrane. The dissolution rate of the blend so prepared was determined and was found to be as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 24.70 |
| 4 | 40.30 |
| 8 | 70.10 |
| 13 | 89.30 |
| 24 | 98.90 |

EXAMPLE 4

Example 3 was repeated except that a sufficient amount of membrane solution (includes solvents) and magnesium stearate was applied to 50 kg of active cores, to achieve a dissolution rate of the pellets (determined in the manner set out in Example 1) as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 0.35 |
| 4 | 5.10 |
| 8 | 33.90 |
| 13 | 69.60 |
| 24 | 95.20 |

An amount of the pellets (85% by weight) so prepared was combined with an amount of active cores (15% by weight), which active cores release all of their diltiazem hydrochloride in approximately 30 minutes and the dissolution rate of the blend so prepared was measured in the manner set out in Example 1 and was found to be as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 11.30 |
| 4 | 15.75 |
| 8 | 49.50 |
| 13 | 81.85 |
| 24 | 96.95 |

EXAMPLE 5

Diltiazem hydrochloride (1.0 kg), adipic acid (0.5 kg) and talc (0.100 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.5 kg) in a standard coating pan using a coating solution of:

| | |
|---|---|
| 10% polyvinylpyrrolidone in isopropanol | 80 parts by weight |
| 5% ethylcellulose in isopropanol | 20 parts by weight |

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds defining active cores were then dried overnight to remove all traces of solvent.

The active cores of the pellets being prepared were then surrounded by a membrane solution consisting of:

| | |
|---|---|
| 5% ethylcellulose in isopropanol | 90 parts by weight |
| 5% polyvinylpyrrolidone in isopropanol | 10 parts by weight |

Each coat of membrane solution comprises 5 ml of solution per kg of coated seeds. After each coat had been applied the pellets were air dried in the coating pan.

The finished pellets were then subjected to a dissolution test. Prior to performing the dissolution test the pellets were dried to evaporate all of the solvent.

The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) according to the procedure of Example 1. The dissolution rate was as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 1.50 |
| 4 | 11.20 |
| 8 | 45.60 |
| 13 | 75.30 |
| 24 | 95.10 |

EXAMPLE 6

Example 5 was repeated except that the coating solution used was:

| | |
|---|---|
| 7.5% cellulose acetate in isopropanol | 20 parts by volume |
| 7.5% polyvinylpyrrolidone in isopropanol | 80 parts by volume |

The membrane suspension used was:

| | |
|---|---|
| 7.5% polyvinylpyrrolidone in isopropanol | 10 parts by volume |
| 7.5% cellulose acetate in isopropanol | 90 parts by volume |
| isopropanol | 100 parts by volume |
| talc | 100 parts by weight |

The dissolution rate of the pellets, which was measured according to the procedure followed in Example 1 was found to be:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 0.10 |
| 4 | 8.50 |
| 8 | 42.10 |
| 13 | 65.70 |
| 24 | 94.50 |

EXAMPLE 7

Example 6 was repeated except that 0.75 kg starch/sugar seeds (0.05-0.6 mm) were used. The coating solution consisted of:

| | |
|---|---|
| 5% EUDRAGIT RL in acetone/isopropanol 40:60 | 80 parts by weight |
| 5% EUDRAGIT RS in acetone/isopropanol 40:60 | 20 parts by weight |

The membrane suspension consisted of:

| | |
|---|---|
| 5% EUDRAGIT RL in acetone/isopropanol 40:60 | 20 parts by weight |
| 5% EUDRAGIT RS in acetone/isopropanol 40:60 | 40 parts by weight |
| 5% EUDRAGIT L in acetone/isopropanol 40:60 | 40 parts by weight |
| Talc | 100 parts by weight |

The membrane suspension was applied and the product dried as in Example 5.

The dissolution rate was as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 0.30 |
| 4 | 12.60 |
| 8 | 54.30 |
| 13 | 79.30 |
| 24 | 99.20 |

EXAMPLE 8

Diltiazem hydrochloride (3.067 kg) was blended together with an amount of sustained release pellets (39.932 kg) prepared in Example 3 along with Avicel pH101 (5.0 kg), cross- linked polyvinylpyrrolidone (1.75 kg) and magnesium stearate (0.25 kg).

The resulting blend was tabletted to obtain a tablet containing 240 mg diltiazem as the hydrochloride salt.

The dissolution rate of the tablets was tested by the method of the U.S. Pharmacopoeia XXI (Paddle Method) according to Example 1.

The dissolution rate was as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 22.6 |
| 4 | 41.5 |
| 8 | 69.8 |
| 13 | 89.5 |
| 24 | 98.9 |

EXAMPLE 9

Diltiazem hydrochloride (3.0 kg), succinic acid (0.35 kg) and talc (0.3 kg) were blended and milled through a No. 100 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.75 kg) in a standard coating pan using a coating solution of:

9% polyvinylpyrrolidone
in isopropanol

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds defining the active cores of the pellet were then dried overnight to remove all traces of solvent.

The active cores of the pellet being prepared were then surrounded by a membrane by applying sequential coats of a suspension consisting of:

| | |
|---|---|
| 12.5% EUDRAGIT RS in acetone/isopropanol 40:60 | 53.33 parts by weight |

(continued)

| | |
|---|---|
| 12.5% EUDRAGIT RL in acetone/isopropanol 40:60 | 13.33 parts by weight |
| Talc | 33.33 parts by weight |

After each coat had been applied the pellets were air dried in the coating pan.

Finished pellets were then subjected to a dissolution test. Prior to performing the dissolution test, the pellets were dried to evaporate all of the solvent. Application of the membrane-forming suspension and drying were continued until the following dissolution profile was obtained.

The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl at pH 7.0 and at 100 r.p.m.

The diltiazem hydrochloride was quantitatively determined using a uv spectrophotometer at 237 nm. The dissolution rate was as follows:

| Time (hours) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 1.7 |
| 4 | 10.7 |
| 8 | 50.6 |
| 13 | 79.9 |
| 24 | 101.4 |

EXAMPLE 10

Pellets were prepared using the ingredients and manufacturing process of Example 9 and having the following dissolution profile.

| Time (h) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 16.7 |
| 4 | 26.9 |
| 8 | 60.6 |
| 13 | 81.7 |
| 24 | 96.5 |

If desired, the same dissolution profile as given in Example 10 can be obtained by blending a proportion (5-20% by weight) of active cores with pellets as prepared in Example 9.

EXAMPLE 11

Example 1 was repeated except that 2.0 kg of diltiazem hydrochloride, 0.5 kg of fumaric acid and 0.2 kg of talc were used and a sufficient amount of membrane solution and talc was applied to achieve the following dissolution profile:

| Time (h) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 1.2 |
| 4 | 0.8 |
| 6 | 5.5 |
| 8 | 16.2 |
| 10 | 32.6 |
| 13 | 55.1 |
| 24 | 98.2 |

EXAMPLE 12

Example 11 was repeated except that a sufficient amount of membrane solution and talc was applied to achieve the following dissolution profile:

| Time (h) | % Diltiazem Hydrochloride released |
|---|---|
| 2 | 0.6 |
| 4 | 0.5 |
| 6 | 1.8 |
| 8 | 8.8 |
| 10 | 22.3 |
| 13 | 45.3 |
| 24 | 94.4 |

EXAMPLE 13

Diltiazem hydrochloride (10.0 kg), fumaric acid (2.5 kg) and talc (1.0 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (5.0 kg) in a standard coating pan using a coating solution of:

| | |
|---|---|
| 10% Polyvinylpyrrolidone in isopropanol | 75 parts by weight |
| 5% Ethylcellulose in methanol/methylene chloride 50/50 | 20 parts by weight |
| 5% Polyvinylchloride in acetone | 4.5 parts by weight |
| Dibutyl phthalate | 0.1 parts by weight |

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds were then dried at 45°C overnight.

The coated seeds defining the active core of the pellets being prepared were then surrounded by an outer mem-

brane consisting of:

| | |
|---|---|
| 5% Eudragit RS in acetone/isopropanol | 80 parts by weight |
| 5% Eudragit RL in acetone/isopropanol | 15 parts by weight |
| 5% Polyvinylchloride in acetone | 5 parts by weight |
| Talc | 99 parts by weight |
| Dibutyl phthalate | 1 part by weight |

A volume equivalent to 5 ml per kg of coated seeds was applied to the seeds in a standard coating pan. After each coat had been applied the pellets were air dried in the coating pan.

At regular intervals the pellets were placed in an oven and allowed to dry for more than twelve hours.

The pellets were then returned to the coating pan and the process of coating, followed by drying to remove solvents, was continued.

The finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl adjusted to pH 7.0 and was found to be as follows:

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 8.7 |
| 6 | 62.8 |
| 13 | 92.0 |

EXAMPLE 14

Example 13 was repeated except starch/sugar seeds 0.5-0.6 mm were used.

The coating solution used was:

| | |
|---|---|
| 17.5% Polyvinylpyrrolidone in isopropanol | 90 parts by weight |
| 10.0% Cellulose acetate in methylene chloride | 10 parts by weight |

The membrane suspension used was:

| | |
|---|---|
| 12.5% Eudragit RS in acetone/isopropanol | 90 parts by weight |
| 12.5% Eudragit RL in acetone/isopropanol | 10 parts by weight |
| Talc | 100 parts by weight |
| Isopropanol | 100 parts by weight |

At regular intervals the pellets were placed in an oven and dried at 55°C for more than twelve hours to remove solvents as in Example 13. The dissolution rate was tested according to the U.S. Pharmacopoeia XXI (Paddle Method). The results were as follows:

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 28.0 |
| 6 | 69.0 |
| 13 | 94.0 |

EXAMPLE 15

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4.0 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder so obtained was applied to starch/sugar seeds (20 kg) 0.5-0.6 mm in diameter, in a FREUND CF granulator using a coating solution of:

9.0% Polyvinylpyrrolidone in isopropanol

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds were then dried at 55°C overnight to remove solvent.

The coated seeds defining the active core of the pellet being prepared were then surrounded by an outer membrane. The membrane suspension used was:

| | |
|---|---|
| 12.5% Eudragit RS in acetone/isopropanol | 80 parts by weight |
| 12.5% Eudragit RL in acetone/isopropanol | 20 parts by weight |
| Talc | 100 parts by weight |
| Isopropanol | 100 parts by weight |

The seeds were then coated in a CF granulator with the membrane suspension and dried at regular intervals at 55°C for 16 hours to remove solvents.

The finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl adjusted to pH 7.0 and was found to be as follows:

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 22.3 |
| 6 | 65.4 |
| 13 | 88.0 |

EXAMPLE 16

Diltiazem hydrochloride (3.0 kg), succinic acid (0.5 kg) and talc (0.3 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.75 kg) in a standard coating pan using a coating solution of:

| | |
|---|---|
| 9% Polyvinylpyrrolidone in isopropanol | 100 parts by weight |

The active cores of the pellet being prepared were then surrounded by a membrane by applying coats of a suspension consisting of:

| | |
|---|---|
| 12.5% EUDRAGIT RS in acetone/isopropanol 40:60 | 20 parts by weight |
| 12.5% EUDRAGIT RL in acetone/isopropanol 40:60 | 20 parts by weight |
| 12.5% EUDRAGIT L in acetone/isopropanol 40:60 | 10 parts by weight |
| Talc | 49 parts by weight |
| Dimethyl phthalate | 1 part by weight |

After each coat had been applied the pellets were air dried in the coating pan. At regular intervals the pellets were placed in an oven and dried at 55°C for more than twelve hours to remove solvent as in Example 13.

Finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of the U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl at pH 7.0 and at 100 r.p.m.

The dissolution rate was as follows:

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 18.9 |
| 6 | 63.4 |
| 13 | 89.6 |

EXAMPLE 17

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a No. 50 mesh screen.

The powder was applied to starch/sugar seeds (0.5-0.6 mm diameter) with a FREUND CF granulator using a coating solution of:

| | |
|---|---|
| 8% Polyvinylpyrrolidone in ethanol | 90 parts by weight |
| 10% Ethocel (Ethocel is a Trade Mark) in isopropanol | 9.8 parts by weight |
| Diethyl phthalate | 0.2 parts by weight |

A membrane was then applied to the active cores by spraying on a suspension consisting of:

| | |
|---|---|
| 12.5% EUDRAGIT RL in acetone/isopropanol 40:60 | 10 parts by weight |
| 12.5% EUDRAGIT RS in acetone/isopropanol 40:60 | 40 parts by weight |

(continued)

| | |
|---|---|
| Isopropanol | 48.75 parts by weight |
| Tributyl citrate | 1.25 parts by weight |

While simultaneously but separately dusting on talc (100 parts by weight) in conventional manner.

A sufficient amount of membrane suspension and talc was applied to achieve a dissolution rate of the pellets, when measured according to U.S. Pharmacopoeia XXI (Paddle Method) as per Example 13, as follows:

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 24.3 |
| 6 | 71.6 |
| 13 | 98.3 |

EXAMPLE 18

Example 16 was repeated except the application solution consisted of:

| | |
|---|---|
| 5% Hydroxypropylmethyl cellulose in methanol/methylene chloride | 99 parts by weight |
| Propylene glycol | 1 part by weight |

and the membrane suspension used was

| | |
|---|---|
| 10% Cellulose acetate in acetone | 90 parts by weight |
| 5% Polyethylene glycol in acetone | 10 parts by weight |

Talc was added as per Example 16.

A sufficient quantity of membrane suspension was applied to the pellets to achieve the following dissolution rate, all pellets having been dried to remove solvents.

| Time (hours) | % Diltiazem hydrochloride released |
|---|---|
| 2 | 13.8 |
| 6 | 61.3 |
| 13 | 88.6 |

EXAMPLE 19

Diltiazem hydrochloride (2.4 kg) and enalapril (0.2 kg) were blended together with an amount of sustained release pellets (41.53 kg) prepared in Example 3 along with Avicel pH101 (5.0 kg), cross-linked polyvinylpyrrolidone (1.75 kg) and magnesium stearate (0.25 kg).

The resulting blend was tabletted to obtain a tablet containing 120 mg of diltiazem hydrochloride and 10 mg of enalapril, which produced a dissolution and bioprofile suitable for once-daily administration of both active ingredients.

EXAMPLE 20

Fumaric acid (2 kg) was size reduced in a conventional pharmaceutical hammer mill through a No. 100 mesh screen. The milled fumaric acid was then blended with captopril (6 kg) for twenty minutes. A solution of polyvinylpyrrolidone (P.V.P.) and ethylcellulose (Ethocel - Ethocel is a Trade Mark) in isopropanol was prepared at concentrations of 15% and 2% of the respective components.

Non-pareil seeds (5 kg) with a particle size of 0.5 to 0.6 mm were placed in a conventional pharmaceutical coating pan. The fumaric acid/captopril blend was applied onto the non-pareil seeds using the P.V.P./Ethocel solution as a binding agent. On completion of this operation the resulting active cores were transferred to a tray drying oven for solvent removal. 10% by weight of active ingredient of the foregoing active cores were mixed with pellets produced according to Example 3 except that the sustained release pellets from said Example contained 90% by weight of diltiazem hydrochloride and said immediate release pellets contained 15% by weight of diltiazem hydrochloride. After blending of the three pellet types they were filled into hard gelatin capsules, so that each capsule contained 120 mg of diltiazem hydrochloride and 50 mg of captopril.

EXAMPLE 21

An amount of pellets as prepared in Example 13 was mixed with an amount of active captopril cores and filled into hard gelatin capsules in a ratio such that the capsule contained 90 mg of diltiazem hydrochloride and 37.5 mg of captopril.

Pharmacological Data for Once-Daily

EXAMPLE 14

In Vivo Performance:

Pharmacological Data for the Diltiazem Formulation of Example 1

The pellet formulation prepared in Example 1 was evaluated in vivo under steady state conditions.

A steady-state study was performed in 12 young healthy male volunteers, comparing the formulation of Example 1 with a reference product (conventional immediate release tablets). The formulation of Example 1 was administered as a single 240 mg encapsulated dose at 0 hours, while the reference was administered as a single 60 mg tablet at 0, 6, 12 and 18 hours (i.e. q.i.d.). Plasma was sampled out to 24 hours and the mean results were calculated and tabulated. The data presented in Table 1 are from day 5 sampling.

TABLE 1

| Mean Diltiazem Concentrations (ng/ml) - Day 5 | | |
|---|---|---|
| Hour | Reference | Formulation of Example 1 |
| 0.00 | 104.08 | 74.83 |
| 0.50 | 104.17 | 75.25 |
| 1.00 | 140.75 | 72.17 |
| 2.00 | 165.42 | 71.75 |
| 3.00 | - | 72.67 |
| 4.00 | 139.83 | 88.42 |
| 6.00 | 107.00 | 95.42 |
| 6.50 | 93.42 | - |
| 7.00 | 107.42 | - |
| 8.00 | 143.58 | 96.92 |
| 10.00 | 138.00 | 107.50 |

TABLE 1 (continued)

| Mean Diltiazem Concentrations (ng/ml) - Day 5 | | |
|---|---|---|
| Hour | Reference | Formulation of Example 1 |
| 12.00 | 94.42 | 106.75 |
| 12.50 | 77.42 | - |
| 13.00 | 87.83 | - |
| 13.50 | 92.58 | - |
| 14.00 | 109.42 | 109.17 |
| 16.00 | 109.00 | 107.75 |
| 18.00 | 82.33 | 96.25 |
| 18.50 | 81.45 | - |
| 19.00 | 94.00 | - |
| 20.00 | 120.33 | 85.00 |
| 22.00 | 117.75 | - |
| 24.00 | 98.92 | 71.08 |

DISCUSSION

The results of this in vivo comparison of the formulation of Example 1 against conventional immediate release tablets (reference) indicate the formulation of

Example 1 to be bioequivalent (85%) to reference (100%). The formulation of Example 1 also exhibits reduced peak to trough fluctuations, thus enabling titration of the dose to safe, consistent and efficacious plasma levels, which is not always seen with more frequently administered immediate release forms of diltiazem. However, the main distinguishing feature is the tmax (time to peak plasma levels) which is considered to be the single most important pharmacokinetic criterion for characterising a specific dosage frequency. The tmax for the formulation of Example 1 is 14.00 hours, thus indicating suitability thereof for once-daily administration, while the tmax for reference is 2.75 hours. Furthermore, when compared to the formulation of Example 1 of our EP-A-0 149 920, a diltiazem formulation for twice-daily administration and having a tmax of 8.7 hours, the extension of tmax achieved with the once-daily formulation of the present invention becomes apparent.

Pharmacological Data for the Diltiazem Formulation of Example 2

METHOD

Subjects:

Six male volunteers participated in the study (Table 2). One subject (Subject 2) dropped out after the second leg of the study for reasons unrelated to participation in the study. All subjects were shown to be healthy during a prestudy physical examination. Volunteers denied use of any medication during the 14 days prior to study initiation.

TABLE 2

| Subject Number | Subject Initials | Age Yrs | Height Cms | Weight (Kg) | Smoker |
|---|---|---|---|---|---|
| 1 | SF | 21 | 171.5 | 72.8 | Yes |
| 2 | NH | 21 | 173.0 | 65.0 | No |
| 3 | LH | 25 | 174.0 | 70.0 | No |
| 4 | PB | 21 | 172.0 | 61.5 | Yes |

TABLE 2 (continued)

| Subject Number | Subject Initials | Age Yrs | Height Cms | Weight (Kg) | Smoker |
|---|---|---|---|---|---|
| 5 | GG | 19 | 180.0 | 74.0 | Yes |
| 6 | TS | 40 | 165.0 | 77.0 | No |

Medication and Dosing

The following medication was used in the study:

(1) Reference 30 mg tablets

(2) Diltiazem 120 mg capsules prepared from a blend of sustained release pellets prepared in Example 2 with 5% of immediate release pellets viz the sustained release pellets without the membrane, hereinafter designated as the formulation of Example 2.

The reference was administered as a 30 mg dose at 0, 6, 12 and 18 hours. The formulation of Example 2 in capsule form was given as a single 120 mg dose at 0 hours.

The studies were designed as a randomized, balanced, single-dose two-way crossover comparison of the reference and the diltiazem formulation of Example 2.

The trial was initially divided into two 24-hour treatment periods. A third 24-hour treatment period was then performed. There were seven days separating each study period. At the time of study entry, subjects were randomly given a study number from 1 to 6, and assigned to treatment schedules based on that study number as shown in Table 3.

Volunteers arrived at the study site 10 to 12 hours before dosing and remained in a fasted state for at least 8 hours before and until 3 hours after dosing. Diet was standardized among treatment periods.

TABLE 3

| Subject Numbers | TREATMENT PERIODS | |
|---|---|---|
| | 1 | 2 |
| 1, 2, 3 | Reference | Formulation of Example 2 |
| 4, 5, 6 | Formulation of Example 2 | Reference |

Plasma diltiazem concentrations were determined by high performance liquid chromatography.

RESULTS

Plasma Diltiazem Concentrations

A summary of the mean results is presented in Table 4.

TABLE 4

| Mean Diltiazem Concentrations (ng/ml) | | |
|---|---|---|
| Time | Reference | Formulation of Example 2 |
| 0.0 | 0.0 | 0.0 |
| 0.5 | 4.02 ± 3.31 | --- |
| 1.0 | 12.98 ± 9.36 | 6.10 ± 2.20 |
| 2.0 | 20.80 ± 11.15 | 6.88 3.17 |
| 3.0 | 23.60 ± 11.15 | --- |

TABLE 4 (continued)

| Mean Diltiazem Concentrations (ng/ml) | | |
|---|---|---|
| Time | Reference | Formulation of Example 2 |
| 4.0 | 22.00 ± 10.25 | 16.32 ± 7.23 |
| 6.0 | 15.68 ± 5.87 | 21.58 ± 13.33 |
| 6.5 | 15.82 ± 7.16 | --- |
| 7.0 | 29.04 ± 15.29 | 30.60 ± 9.55 |
| 8.0 | 38.00 ± 10.46 | 35.80 ± 13.39 |
| 9.0 | --- | 40.80 ± 18.90 |
| 10.0 | 32.00 ± 7.97 | 46.20 ± 20.78 |
| 12.0 | 21.60 ± 6.39 | 54.60 ± 26.43 |
| 12.5 | 18.40 ± 6.66 | --- |
| 13.0 | 21.76 ± 9.10 | --- |
| 14.0 | 33.60 ± 14.47 | 56.00 ± 25.42 |
| 16.0 | 34.60 ± 11.72 | 45.60 ± 16.96 |
| 18.0 | 26.80 ± 5.97 | 39.20 ± 13.99 |
| 18.5 | 26.60 ± 7.33 | --- |
| 19.0 | 27.40 ± 12.92 | --- |
| 20.0 | 38.20 ± 17.02 | 28.40 ± 5.27 |
| 22.0 | 34.20 ± 9.88 | --- |
| 24.0 | 33.20 ± 14.86 | 22.80 ± 7.29 |
| 28.0 | 17.02 ± 4.75 | --- |
| 36.0 | 2.58 ± 3.55 | 3.54 ± 3.38 |

DISCUSSION

The purpose of the studies carried out was to compare the pharmacokinetic profiles of a controlled absorption formulation of diltiazem according to the invention with divided doses of a reference product. The formulation of Example 2 was especially designed for once-daily administration of diltiazem and it was anticipated that this formulation would demonstrate a plasma profile consistent with this reduced dosage frequency.

The results of the study confirm the delayed and extended plasma profile of the formulation of Example 2. Although the product of Example 2 contains a proportion of immediate-release component (5%), the product demonstrated a significantly delayed time to peak plasma diltiazem concentrations compared with the reference. Mean trough levels were very similar for both products with no significant differences in mean blood concentrations at 24 hours post administration for the product of Example 2 relative to the reference, further emphasizing the prolonged absorption nature of the formulation according to the invention.

The elimination characteristics of the formulation of Example 2 were also consistent with a once-daily plasma profile. The formulation of Example 2 showed a considerably slower apparent elimination rate and longer apparent half-life value compared with the reference.

Estimates of relative bioavailability showed the formulation of Example 2 to be more bioavailable than the reference product demonstrating 112.06% relative bioavailability based on 24 hour data.

The formulation of Example 2 attained a remarkably extended tmax of 13.20 hours after administration as compared to 2.30 hours for reference and 8.7 hours for the formulation of Example 1 of our EP-A-0 149 920, which is a diltiazem formulation suitable for twice-daily administration. This extension in tmax thus shows the formulation of Example 2 to meet the criteria for once-daily administration and the overall results of the study demonstrate the achievement of a once-daily profile for the product of Example 2.

Pharmacological Data in respect of the Formulation of Example 3

The blend of pellets prepared in Example 3 was filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was compared with a single dose of pellets in capsule form and which pellets are prepared in accordance with Example 1 of our EP-A-0 149 920 (twice-daily form of diltiazem) and identified hereinafter as "twice-daily formulation" administered as a single dose in six subjects. The two different formulations were tested in the same group of six subjects. The mean blood levels of the two formulations were determined and are shown in Table 5.

TABLE 5

| Time(h) | Twice-daily Formulation Blood Level (ng/ml) | Time(h) | Formulation of Example 3 Blood Level (ng/ml) |
|---|---|---|---|
| 0.00 | 0.00 | 0.00 | 0.00 |
| 1.00 | 0.00 | 1.00 | 11.20 |
| 2.00 | 2.17 | 2.00 | 12.30 |
| 4.00 | 29.67 | 4.00 | 17.97 |
| 5.00 | 52.33 | 5.00 | 22.67 |
| 6.00 | 63.67 | 6.00 | 28.67 |
| 7.00 | 69.00 | 7.00 | 32.33 |
| 8.00 | 69.50 | 8.00 | 36.17 |
| 9.00 | 62.50 | 9.00 | 38.50 |
| 10.00 | 53.83 | 10.00 | 44.50 |
| 12.00 | 38.67 | 12.00 | 41.67 |
| 14.00 | 27.17 | 14.00 | 35.33 |
| 16.00 | 20.17 | 16.00 | 28.33 |
| 18.00 | 15.22 | 18.00 | 23.00 |
| 20.00 | 12.95 | 20.00 | 18.33 |
| 24.00 | 7.70 | 24.00 | 12.77 |

Time of Maximum Blood Levels (tmax)

The time of maximum blood levels (h) (tmax) was observed for each subject and each formulation. The mean tmax values were as follows:

| | | |
|---|---|---|
| Twice-daily formulation | Mean tmax = 7.17 | Based on 6 subjects |
| Formulation of Example 3 | Mean tmax = 10.67 | Based on 6 subjects |

DISCUSSION

In the study, the formulation of Example 3 was compared with a formulation prepared as per Example 1 of our EP-A-0 149 920 which is an effective formulation for twice-daily administration of diltiazem. Whilst the "twice-daily" formulation achieves a notable extension in tmax (7.17 hours) as compared to conventional immediate release diltiazem, it does not exhibit a pharmacokinetic profile consistent with once-daily administration. However, the formulation of Example 3 demonstrates a lower peak to trough ratio than, while being bioequivalent (93.5%) to, the twice-daily formulation (100%). Most importantly, however, is the significantly extended tmax obtained (10.67 hours) with the formulation of Example 3, thus demonstrating an overall pharmacokinetic profile consistent with once-daily administration.

Pharmacological Data for the Diltiazem Hydrochloride Formulation prepared in Example 4

The blend of pellets prepared in Example 4 was filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was compared with conventional reference tablets (30 mg) hereinafter referred to as reference administered four times daily in six subjects. The two different formulations were tested in the same group of six subjects.

The meant blood levels of the two formulations were determined and are shown in Table 6.

TABLE 6

| Time(h) | Reference Blood Level (ng/ml) | Time(h) | Formulation of Example 4 Blood Level (ng/ml) |
|---|---|---|---|
| 0.00 | 0.00 | 0.00 | 0.00 |
| 0.50 | 4.33 | 0.50 | 0.00 |
| 1.00 | 6.40 | 1.00 | 10.42 |
| 1.50 | 12.52 | 2.00 | 17.63 |
| 2.00 | 18.65 | 4.00 | 15.07 |
| 4.00 | 22.17 | 6.00 | 21.22 |
| 6.00 | 12.07 | 7.00 | 23.38 |
| 6.50 | 10.62 | 8.00 | 27.30 |
| 7.00 | 21.47 | 10.00 | 33.67 |
| 7.50 | 30.83 | 12.00 | 39.83 |
| 8.00 | 29.00 | 14.00 | 40.83 |
| 10.00 | 31.17 | 16.00 | 33.83 |
| 12.00 | 16.97 | 20.00 | 25.17 |
| 12.50 | 15.65 | 24.00 | 20.13 |
| 13.00 | 15.42 | 36.00 | 4.62 |
| 13.50 | 25.00 | 0.00 | 0.00 |
| 14.00 | 29.50 | 0.00 | 0.00 |
| 16.00 | 30.30 | 0.00 | 0.00 |
| 18.00 | 21.93 | 0.00 | 0.00 |
| 18.50 | 25.00 | 0.00 | 0.00 |
| 18.90 | 26.33 | 0.00 | 0.00 |
| 19.50 | 29.65 | 0.00 | 0.00 |
| 20.00 | 37.83 | 0.00 | 0.00 |
| 22.00 | 35.33 | 0.00 | 0.00 |
| 24.00 | 28.83 | 0.00 | 0.00 |

Time of Maximum Blood Levels (tmax)

The time of maximum blood levels (h) (tmax) was observed for each subject and each formulation.

The mean tmax values were as follows:

| | | |
|---|---|---|
| Reference | Mean tmax = 2.58 | Based on 6 subjects |
| Formulation of Example 4 | Mean tmax = 13.00 | Based on 6 subjects |

DISCUSSION

The formulation of Example 4 demonstrated a remarkably extended in vivo tmax (13.00 hours) as compared to reference (2.58 hours). Furthermore, the formulation of Example 4 was bioequivalent (100%) to conventional immediate release tablets administered every six hours (100%). Based on this overall pharmacokinetic profile, the formulation of Example 4 is eminently suitable for once-daily oral administration.

Pharmacological Data in respect of the Formulation of Examples 11 and 12

The pellets prepared in Examples 11 and 12 were filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was administered as a single dose in five subjects. The time of maximum blood levels (h) (tmax) was observed for each subject and formulation and the mean tmax value for Example 11 was 17.8 and the mean tmax value for Example 12 was 18.6.

Pharmacological Data for Twice-Daily Diltiazem Formulations

In vivo Performance:

Pharmacological Data for the Diltiazem Formulation of Example 13

A single-dose crossover study was performed in 6 young healty male subjects comparing the formulation of Example 13 against the formulation of Example 1 of our EP-A-0 149 920 (hereinafter referred to as Reference). Both the formulation of Example 13 and the Reference formulation were administered as a single encapsulated dose of 120 mg at 0 hours. Plasma concentration of diltiazem was determined at intervals over 24 hours and the results are illustrated in Fig. 1.

Fig. 1 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 13 (curve a) compared with a single dose (120 mg) of the Reference formulation (curve b). As will be appreciated, the data for the Reference formulation was obtained from a different group of subjects to that of present Example 13, thus making any comparison of bioavailability purely indicative. It will be observed from Fig. 1 that a virtually identical absorption pattern is obtained for each formulation, consistent with twice-daily administration. Hence it is submitted the actual bioavailability values would have been similar if the two formulations had been tested in the same subjects.

Pharmacological Data for the Diltiazem Formulation of Example 14

A single-dose crossover study was performed in 6 young healthy male subjects comparing the formulation of Example 14 against the formulation of Example 1 of our EP-A-0 149 920 (hereinafter referred to as Reference). Both formulations were administered as a single 120 mg capsule at 0 hours. Plasma concentration of diltiazem was determined at intervals over 24 hours and the results are illustrated in Fig. 2.

Fig. 2 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 14 (curve a) compared with a single dose (120 mg) of the Reference formulation (curve b). As in the case of the pharmacological data for the formulation of Example 13 compared with the Reference, the data for the Reference formulation were obtained from a different group of subjects to that of present Example 14, thus making any comparison of bioavailability purely indicative. It will be observed from Fig. 2 that a virtually identical absorption pattern is obtained for each formulation, consistent with twice-daily administration. Hence it is submitted the actual bioavailability values would have been similar if the two formulations had been tested in the same subjects.

Pharmacological Data for the Diltiazem Formulation of Example 15

A steady-state crossover study was performed in 12 young healthy male subjects comparing the formulation of

Example 15 against conventional immediate release tablets (Reference tablets).

The formulation of Example 15 was administered as a single 120 mg capsule at 0 and 12 hours (b.i.d.), while the Reference was administered as a single 60 mg tablet of 0, 6, 12 and 18 hours (q.i.d.). Plasma concentration of diltiazem was measured at intervals over 24 hours on Day 5 and the results are illustrated in Fig. 3. Pharmacokinetic data are given in Table 7.

TABLE 7

| PHARMACOKINETIC EVALUATION (n=6) | | |
|---|---|---|
| Parameters | Reference Tablets | Formulation of Example 15 |
| AUC (0-24h) | 2474.88 | 2230.33 |
| F (t) % | 100.00 | 90.96 |
| Cmax | 172.08 | 130.42 |
| Tmax | 2.75 | 4.17 |

Fig. 3 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 3 (curve a) compared with a single dose (60 mg) of reference tablets administered as indicated above.

It will be observed from the data presented in Table 7 that the formulation of Example 15 is 90.96% bioavailable compared to Reference (= 100%), and has a quite similar Cmax and AUC (0-24h). However, the formulation of Example 15 has extended tmax (4.17 hours compared to 2.75 hours for Reference) which satisfies the criteria for controlled absorption orally administered drugs, and further shows a reduction in peak-to-trough fluctuations as indicated in Fig. 3.

Experiments were carried out to assess the stability of the pellet formulation according to the invention relative to formulations of our EP-A-0 149 920.

Dissolution tests of the type described in Example 13 were carried out on a batch of the pellet formulation of Example 15 after storage in ambient conditions over a period concomitant with commercial shelf-life, in accordance with established criteria. The results are presented in Fig. 4 which is a graph of dissolution (%) versus time (hours) taken at three different time points after manufacture of the formulation of Example 15 under the indicated conditions and is indicative of the stability of the formulation under these conditions. In Fig. 4 curve a represents the batch as tested after 3 months of storage, curve b the batch as tested after 6 months storage and curve c the batch as tested after 18 months storage.

Dissolution tests of the type described in Example 13 were also carried out on a batch of the pellet formulation of Example 15 under 'accelerated conditions' (37°C and 75% relative humidity) in accordance with established criteria. The results are presented in Fig. 5 which is a graph of dissolution (%) versus time (hours) taken at three different time points after the manufacture of the formulation of Example 15 under the indicated conditions and is indicative of the stability of the formulation under these conditions. In Fig. 5 curve a represents the batch as tested after 1 month of storage, curve b the batch as tested after 3 months of storage and curve c the batch as tested after 6 months of storage.

Identical dissolution tests under identical accelerated conditions were carried out on a batch of a pellet formulation prepared in accordance with Example 1 of our EP-A-0 149 920. The results are presented in Fig. 6 which again is a graph of dissolution (%) versus time (hours) taken at three different time points after the manufacture of the formulation in question. In Fig. 6 curve a represents the batch as tested after 1 month of storage, curve b the batch as tested after 3 months of storage and curve c the batch as tested after 6 months of storage. A comparison of Figs. 4, 5 and 6 demonstrates the stability of the formulation of the present invention relative to the formulation of our EP-A-0 149 920. As will be observed the formulation of EP-A-0 149 920 under the specified conditions is unstable and therefore if commercially used would require excessive inventory control procedures.

The formulations according to the invention, which are characterised by specific in vitro dissolution rates and a more controlled manufacturing process, have excellent stability over the normal marketing shelf-life (18 months to 2 years) in terms of both in vivo and in vitro performance.

## Claims

1. A controlled absorption diltiazem pellet formulation for oral administration, said pellet comprising a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, the diltiazem component and the organic acid being present in a ratio of from 50:1 to 1:1, and a multi-layer membrane surrounding said core and

containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble synthetic polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said diltiazem from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a twelve hour period following oral administration, said rate being measured in vitro as a dissolution rate of said pellet, which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) no more than 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) no more than 60% of the total diltiazem is released after 4 hours of measurement in said apparatus; and
c) 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

2. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 0 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 10 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 25 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

3. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 5 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

4. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twelve hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 35 to 85% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) 100% of the total diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

5. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twelve hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 55 to 80% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

6. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 5, wherein the core comprises:

a) a powder mixture containing diltiazem or a pharmaceutically acceptable salt thereof, an organic acid selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble synthetic polymer and a minor proportion of a pharmaceutically acceptable water insoluble synthetic polymer, said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

7. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 6, wherein the water soluble polymer in the core or membrane is the same or different and is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or polyethylene glycol or a mixture thereof.

8. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 6, wherein the water soluble polymer in the core or membrane is replaced by a polymeric material which is freely permeable to diltiazem and water and comprises a copolymer of acrylic and methacrylic acid esters.

9. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 8, wherein the water insoluble polymer in the core or membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate poly (ethyl methacrylate), poly(butyl methacrylate), poly (isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

10. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 8, wherein the water insoluble polymer in the core or membrane is replaced by a polymeric material which is slightly permeable to diltiazem and water and comprises a copolymer of acrylic and methacrylic acid esters.

11. A process for the production of a controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 10, which comprises forming a core of diltiazem, or a pharmaceutically acceptable salt thereof, an organic acid and other optional components and enclosing the core in a membrane of a film-forming polymer or mixture thereof as defined in Claim 1 which permits release of the diltiazem or the pharmaceutically acceptable salt thereof in the manner set out in any one of Claims 1 to 5.

12. A controlled absorption diltiazem formulation for oral administration comprising pellets according to any one of Claims 1 to 3 or any one of Claims 6 to 10 when dependent on any one of Claims 1 to 3, said formulation including a sufficient quantity of a rapid release form of diltiazem so as to have a dissolution rate which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 10 to 60% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 90% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 100% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

13. A controlled absorption formulation for oral administration comprising pellets according to any one of Claims 1 to 10 and 12, further comprising an ACE-inhibitor or a pharmaceutically acceptable salt thereof, said ACE-inhibitor preferably being selected from captopril, fosenopril, enalapril, ramipril, zofenopril, quinapril, cilazapril, spirapril, lisinopril, delapril, pivalopril, fentiapril, indolapril, alacepril, tiapamil (N-(3,4-dimethoxyphenethyl)-3-[2-(3,4- dimethoxyphenyl)-1 3-dithian-2-yl]-N-methylpropylamine 1,1,3,3-tetraoxide), pentopril, rentiapril and perindopril.

14. Use of diltiazem or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control of hypertension and the symptoms of angina over a twenty-four hour period following administration of a single

therapeutically effective dose thereof.

15. Use according to Claim 14, wherein there is administered once-daily in combination or concomitantly with the diltiazem or pharmaceutically acceptable salt thereof a single therapeutically effective dose of an ACE-inhibitor.

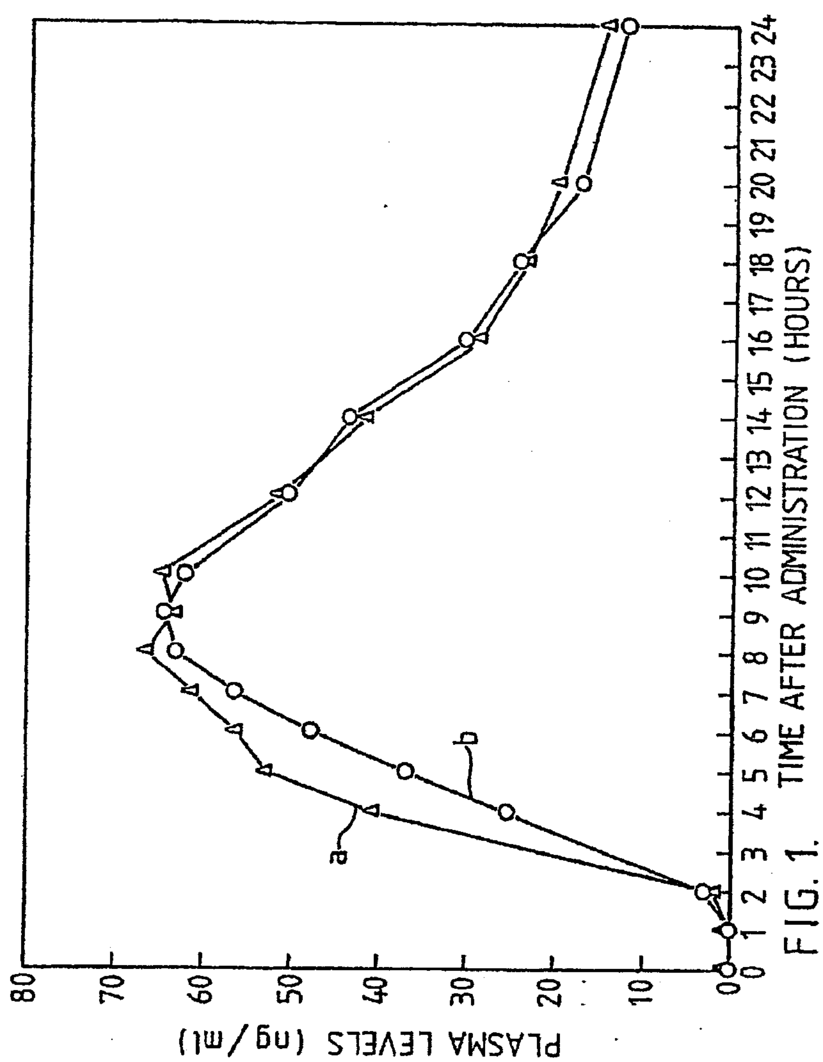
PLASMA LEVELS (ng/ml)
0
10
20
30
40
50
60
70
80
TIME AFTER ADMINISTRATION (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
a
b

FIG. 1.

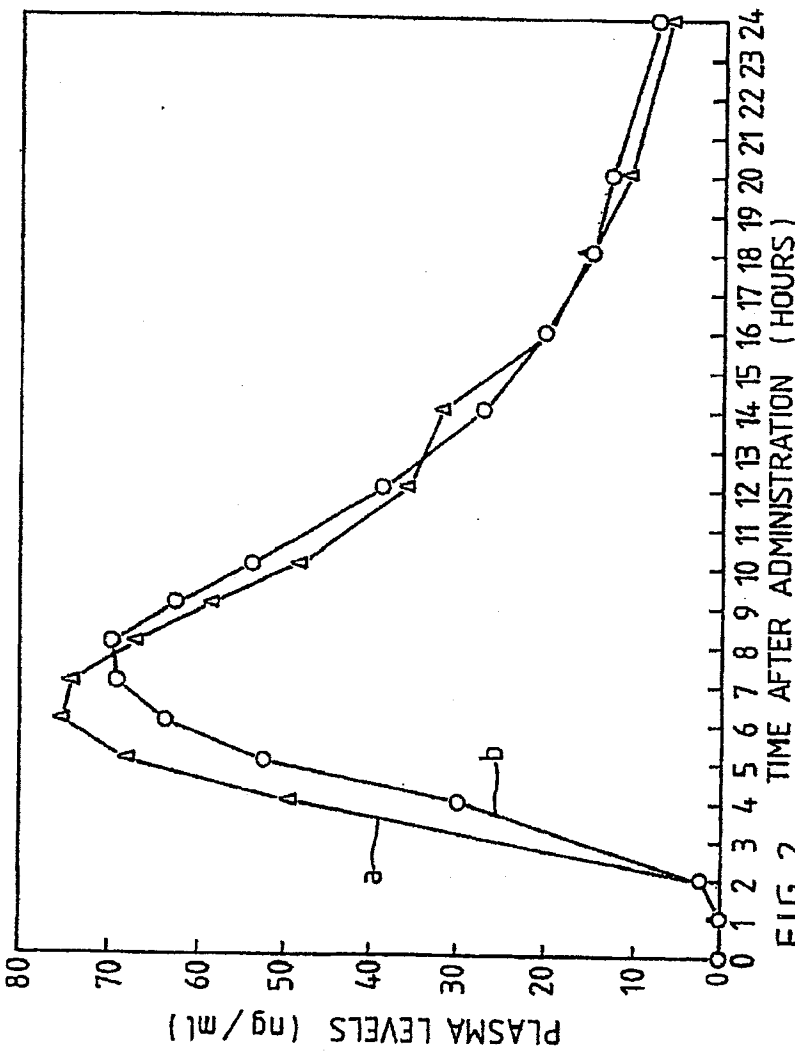
PLASMA LEVELS (ng/ml)
0
10
20
30
40
50
60
70
80
TIME AFTER ADMINISTRATION (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
a
b

FIG. 2.

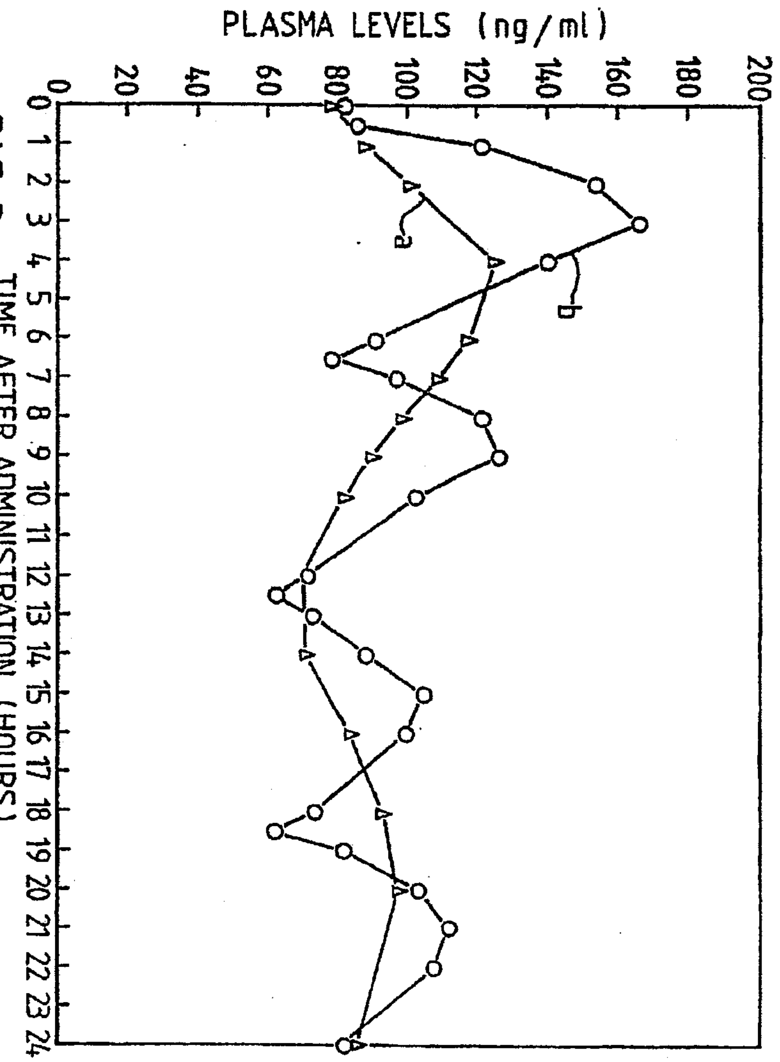
PLASMA LEVELS (ng/ml)
0
20
40
60
80
100
120
140
160
180
200
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME AFTER ADMINISTRATION (HOURS)
a
b

FIG. 3.

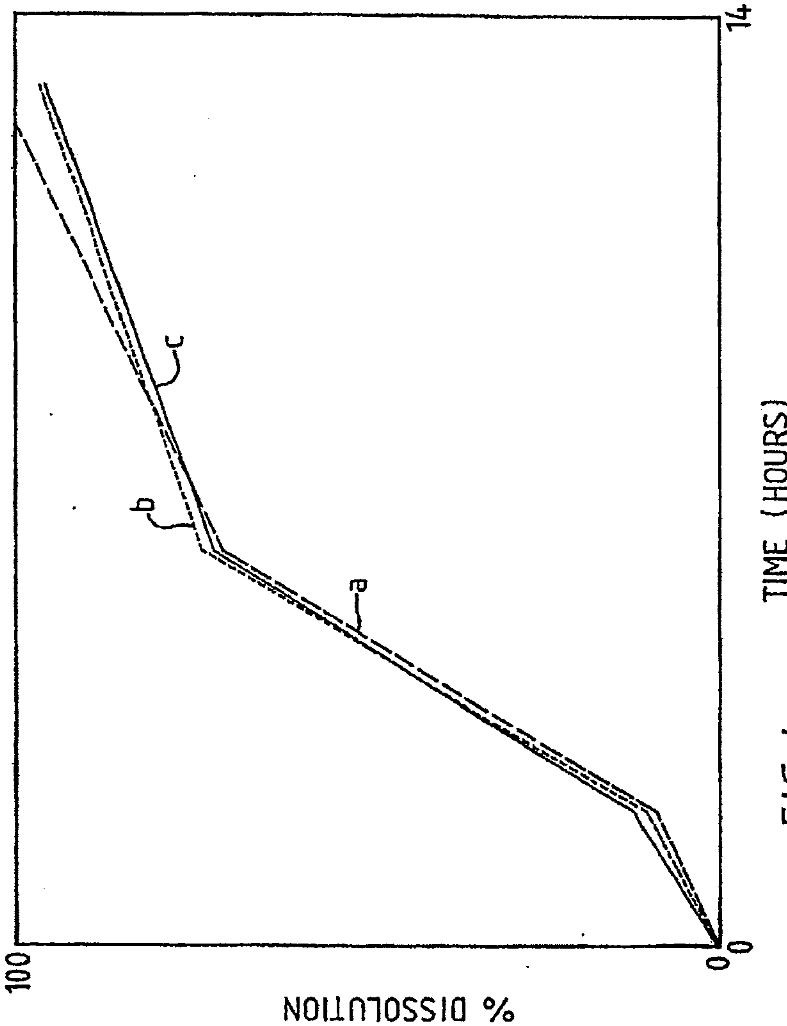


FIG. 4.

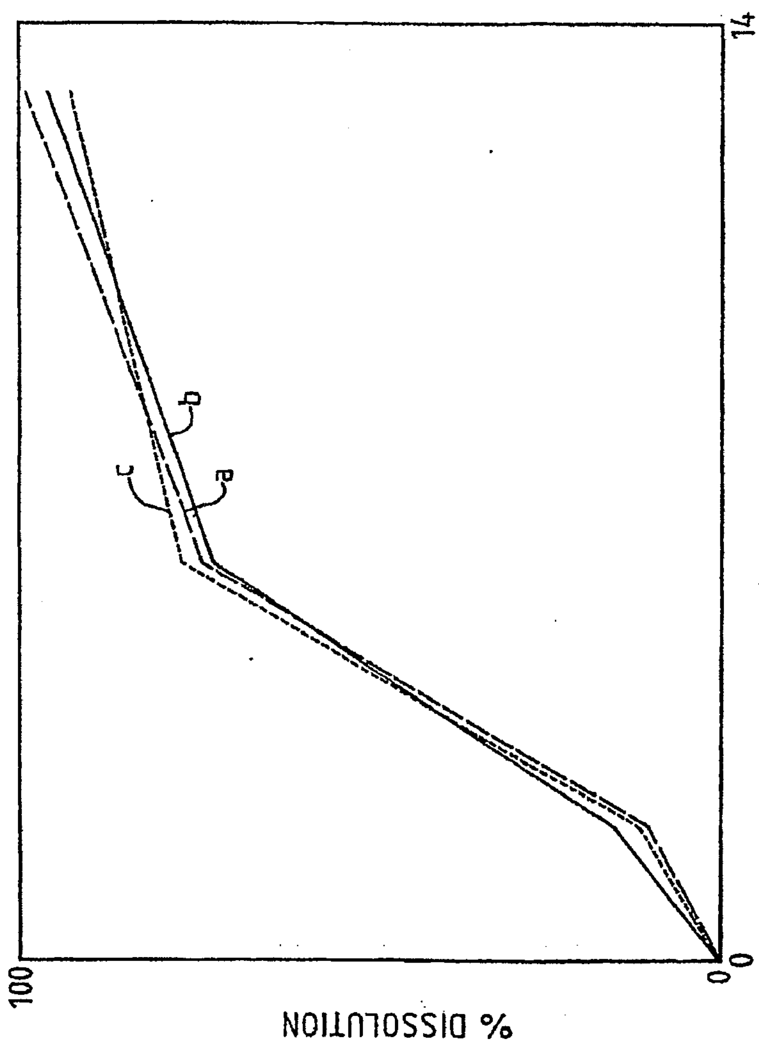


FIG. 5.

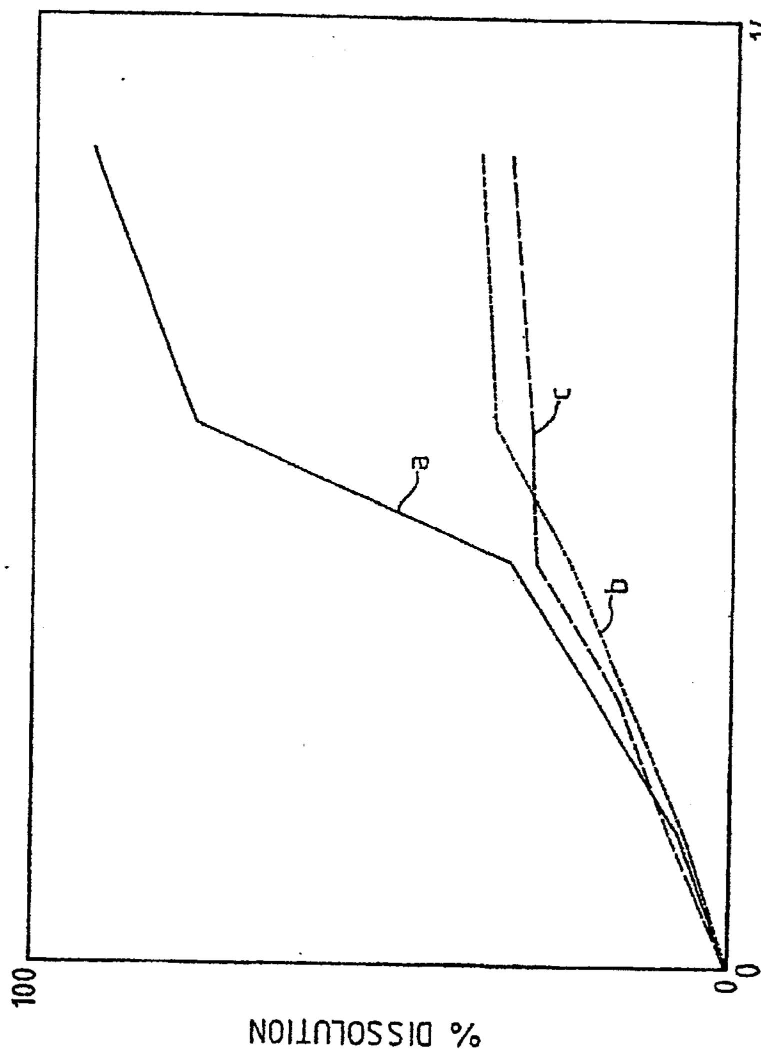


FIG. 6.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number
EP 98 10 5888

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
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| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
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| Y | EP 0 077 956 A (TANABE) 4 May 1983<br>* page 11 *<br>* page 21 - page 22 *<br>* claims * | 1-12 | |
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The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| BERLIN | 14 May 1998 | Alvarez Alvarez, C |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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